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(12) **United States Patent**
Taylor et al.(10) **Patent No.:** **US 9,284,283 B2**
(45) **Date of Patent:** **Mar. 15, 2016**(54) **MACROCYCLIC COMPOUNDS FOR
MODULATING IL-17***A61K 31/33* (2006.01)
A61K 31/44 (2006.01)
A61K 31/445 (2006.01)
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(Continued)

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Lexington, MA (US)(52) **U.S. Cl.**CPC *C07D 257/10* (2013.01); *A61K 31/366*
(2013.01); *A61K 31/42* (2013.01); *A61K 38/00*
(2013.01); *C07D 255/02* (2013.01); *C07D*
257/02 (2013.01); *C07D 273/00* (2013.01);
C07D 401/12 (2013.01); *C07D 403/12*
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409/12 (2013.01); *C07D 409/14* (2013.01);
C07D 413/12 (2013.01); *C07D 417/12*
(2013.01)(58) **Field of Classification Search**USPC 514/255.05, 183, 256, 278, 326, 365,
514/374, 444, 451; 540/453, 460, 461
See application file for complete search history.(56) **References Cited**

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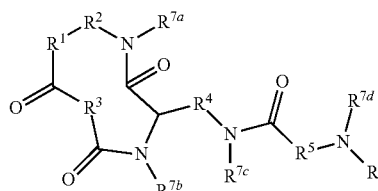
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Primary Examiner — Kristin Vajda(74) *Attorney, Agent, or Firm* — Goodwin Procter LLP(57) **ABSTRACT**The invention relates generally to macrocyclic compounds of
formula I and their therapeutic use. More particularly, the
invention relates to macrocyclic compounds that modulate
the activity of IL-17 and/or are useful in the treatment of
medical conditions, such as inflammatory diseases and other
IL-17-associated disorders.

(I)



16 Claims, 284 Drawing Sheets

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C07D 403/12 (2006.01)
C07D 417/12 (2006.01)
A61K 31/4965 (2006.01)**Related U.S. Application Data**(60) Provisional application No. 61/593,993, filed on Feb.
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(2) Date: **Aug. 1, 2014**(87) PCT Pub. No.: **WO2013/116682**PCT Pub. Date: **Aug. 8, 2013**(73) Assignee: **Ensemble Therapeutics Corporation**,
Cambridge, MA (US)(*) Notice: Subject to any disclaimer, the term of this
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U.S.C. 154(b) by 0 days.

- (51) **Int. Cl.**
A61K 31/42 (2006.01)
A61K 31/38 (2006.01)
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A61K 38/00 (2006.01)
A61K 31/366 (2006.01)
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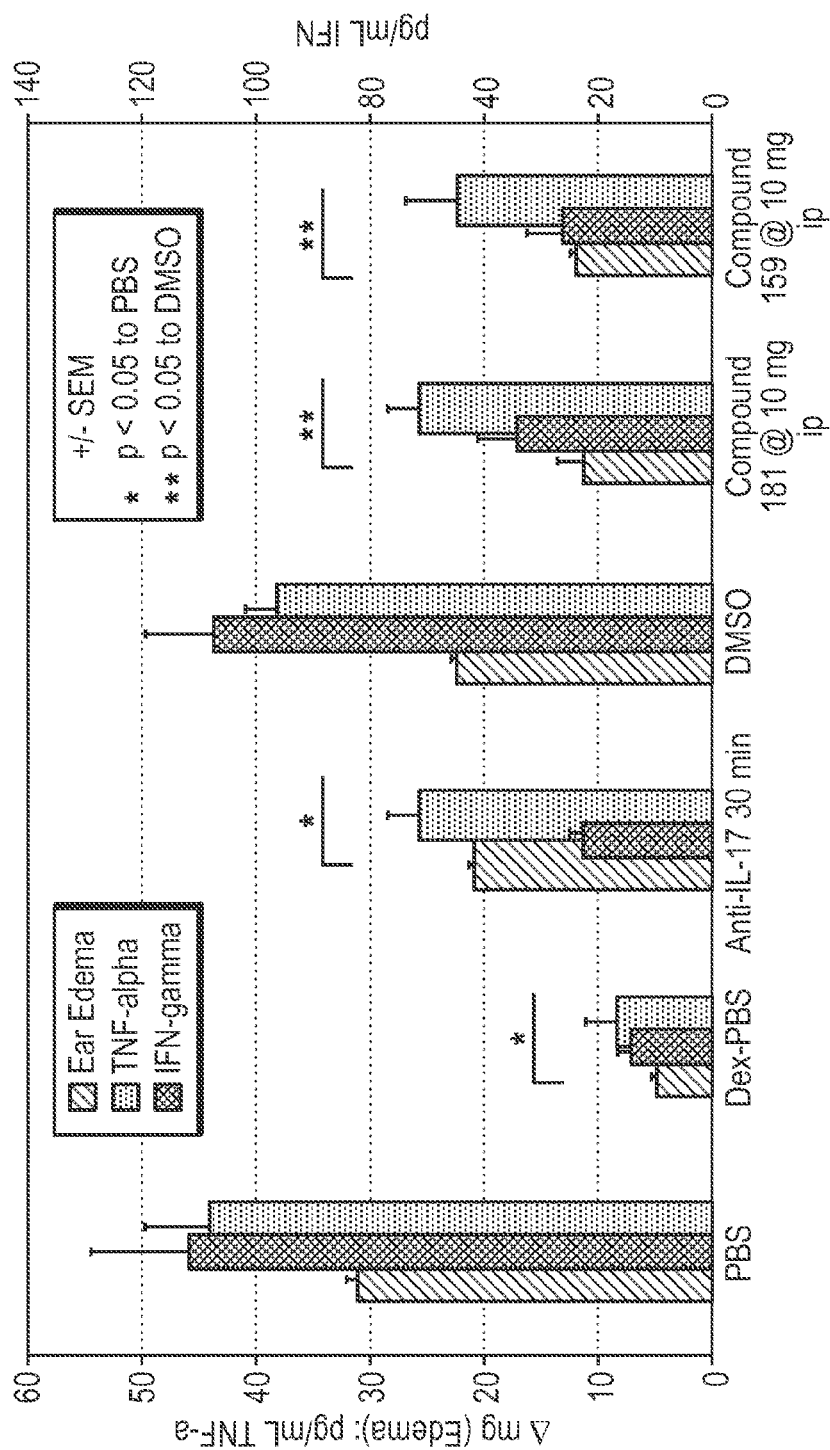


FIG. 1

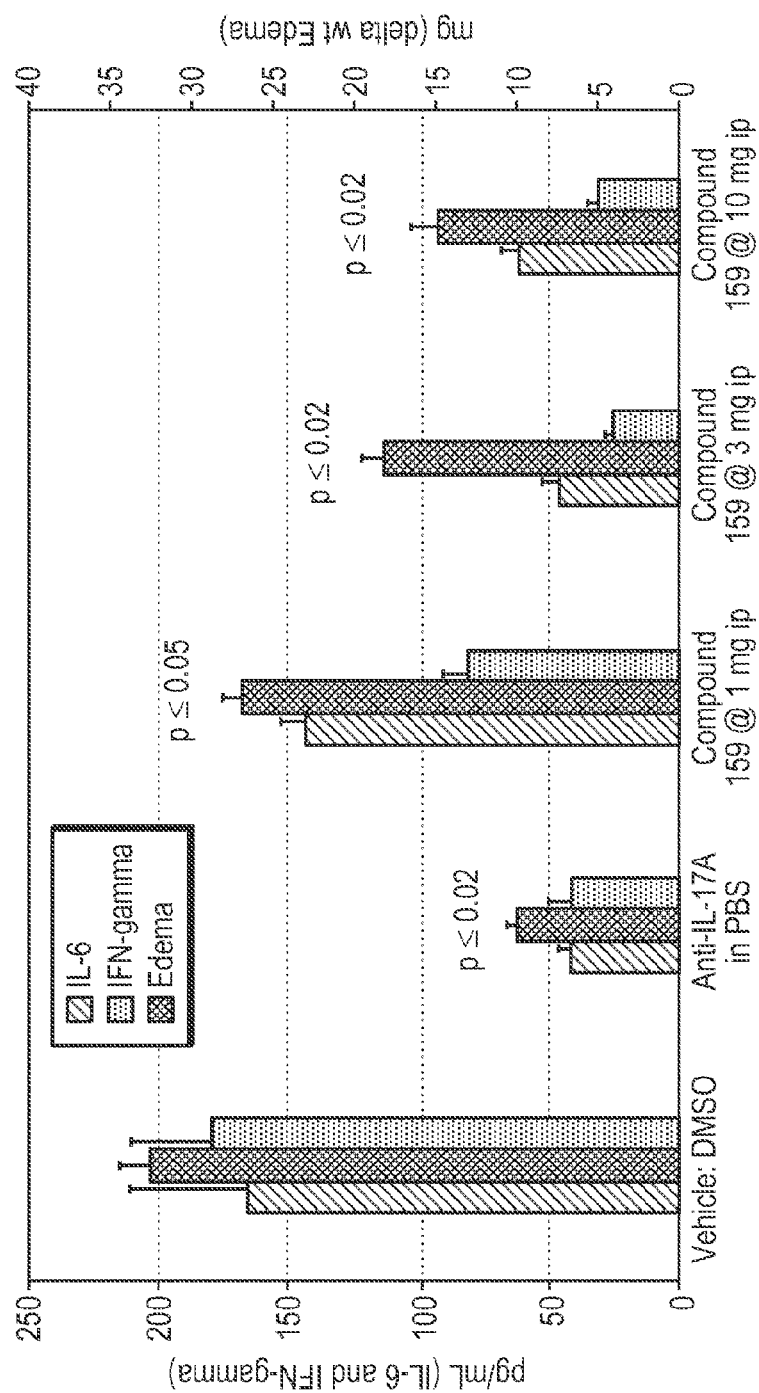


FIG. 2

FIG. 3

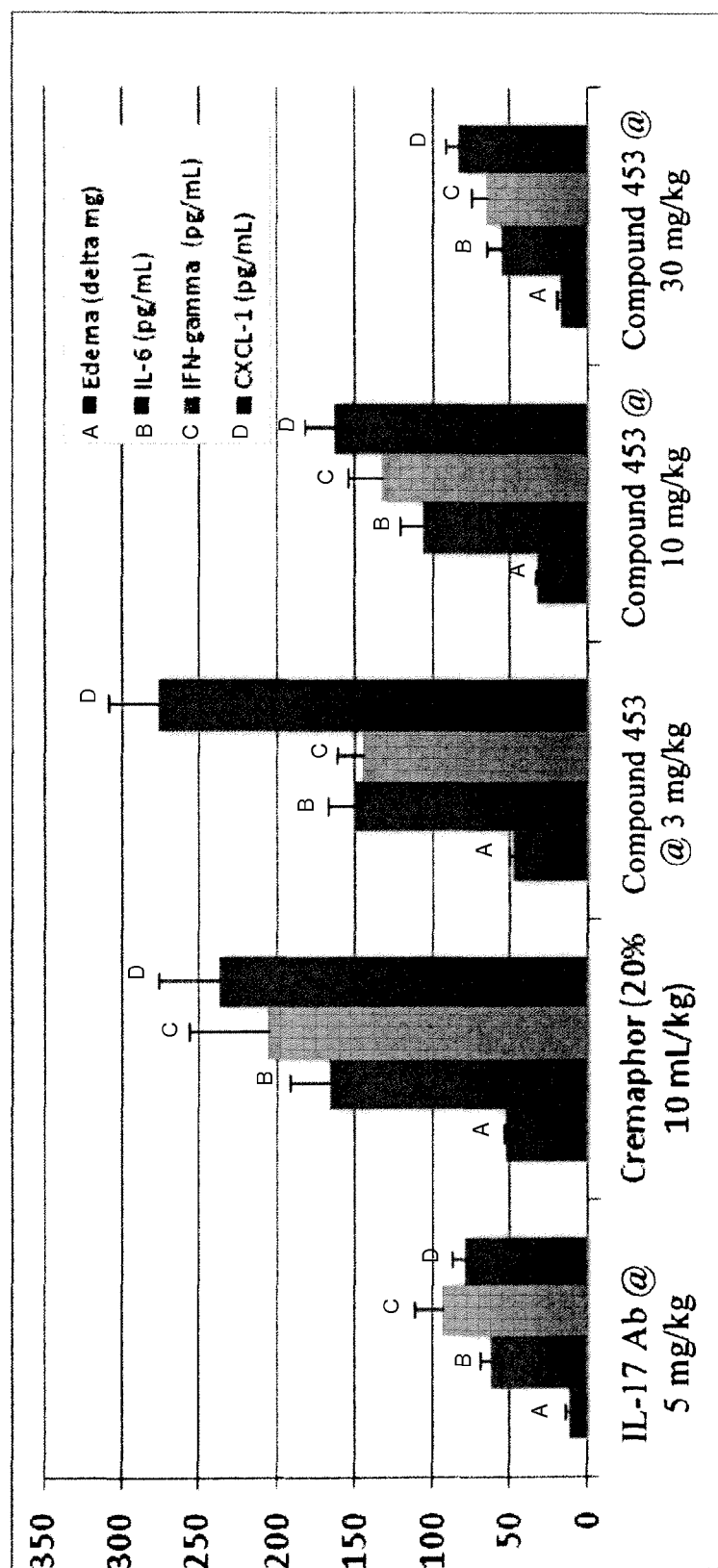


FIG. 4

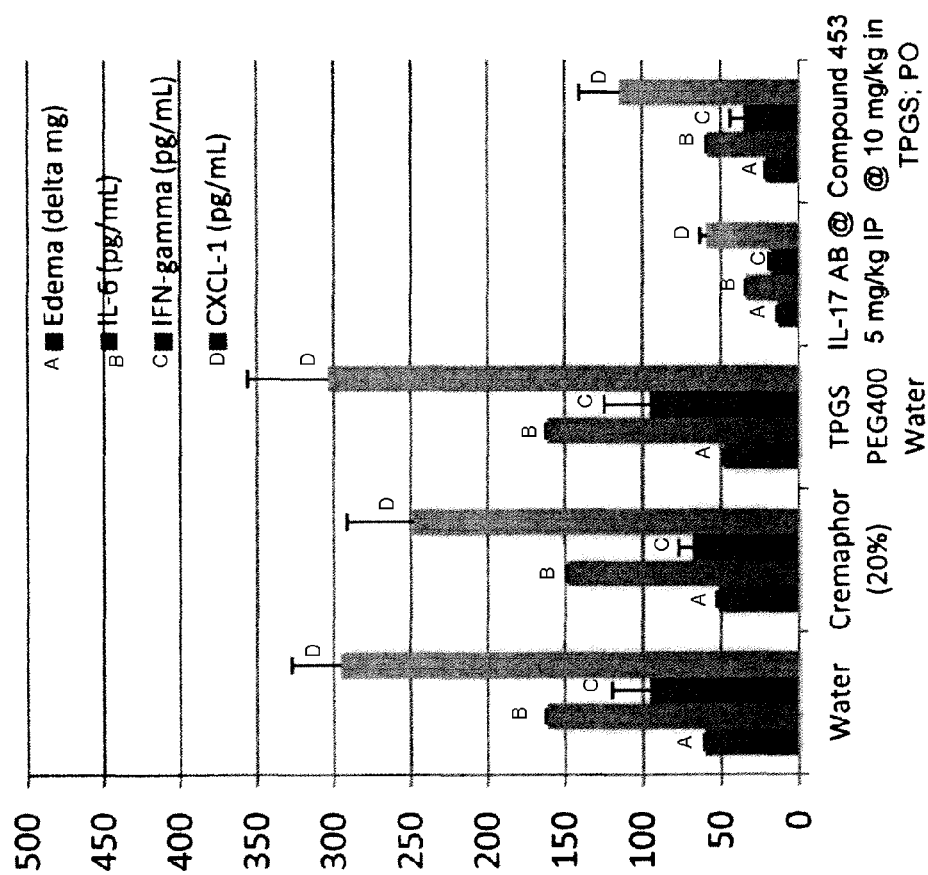
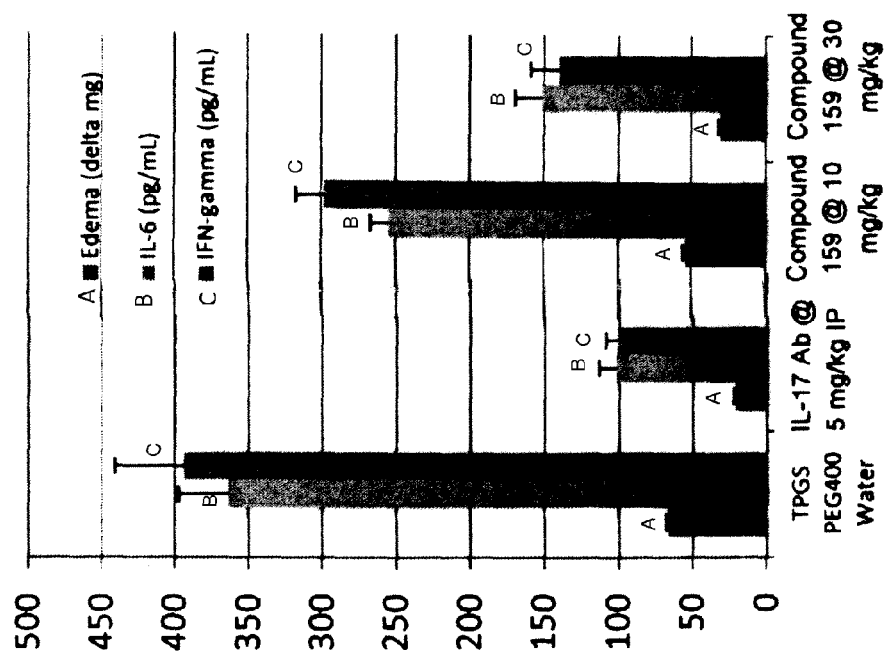


FIG. 5



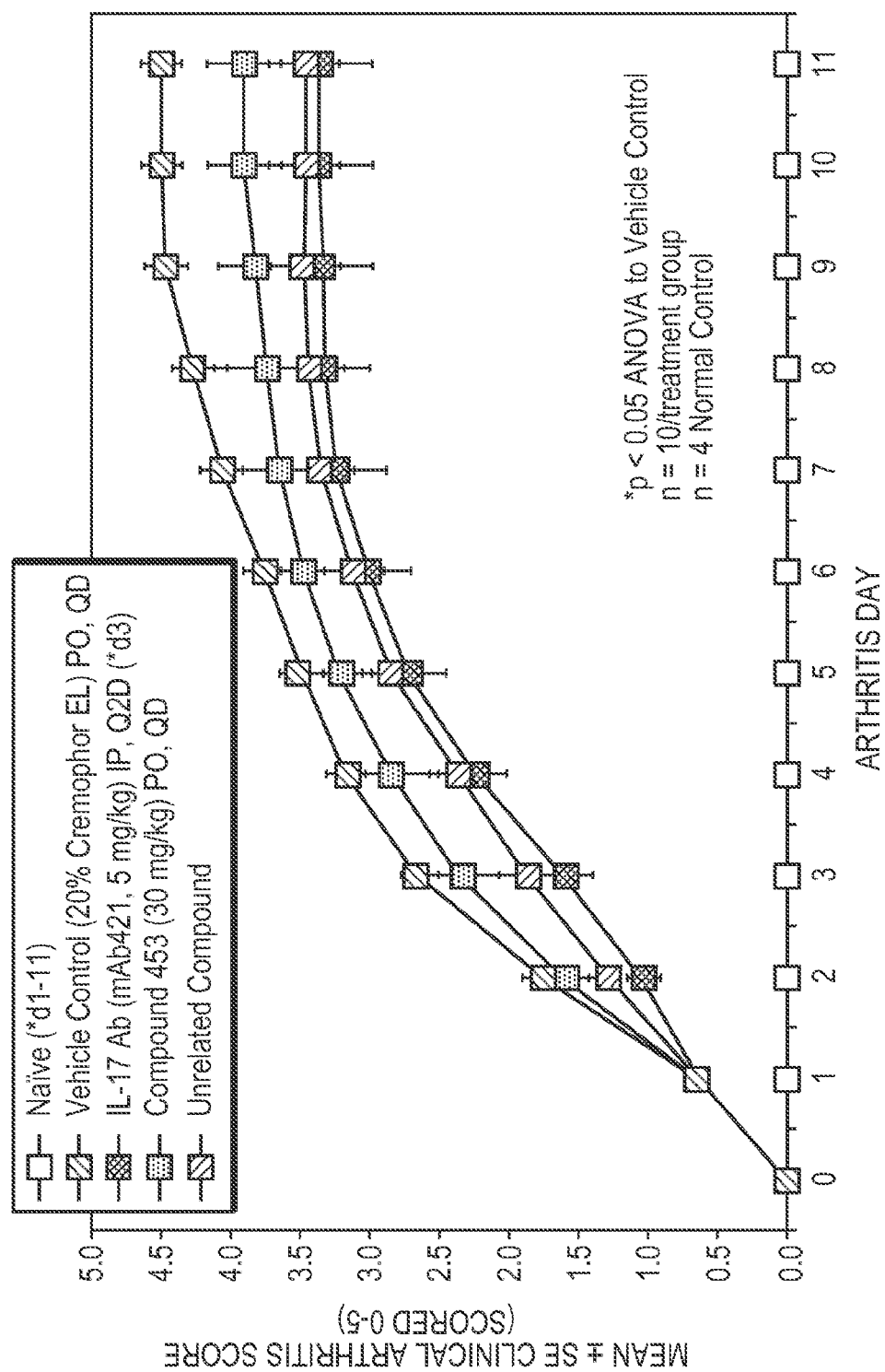


FIG. 6

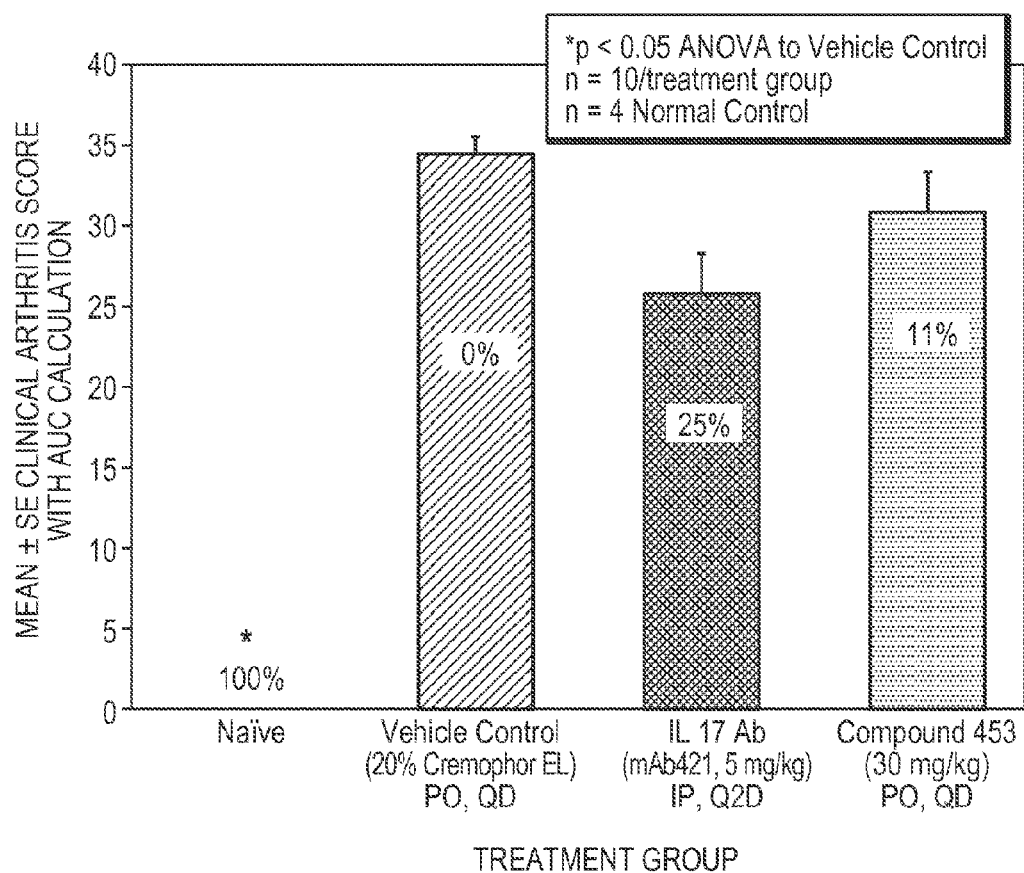
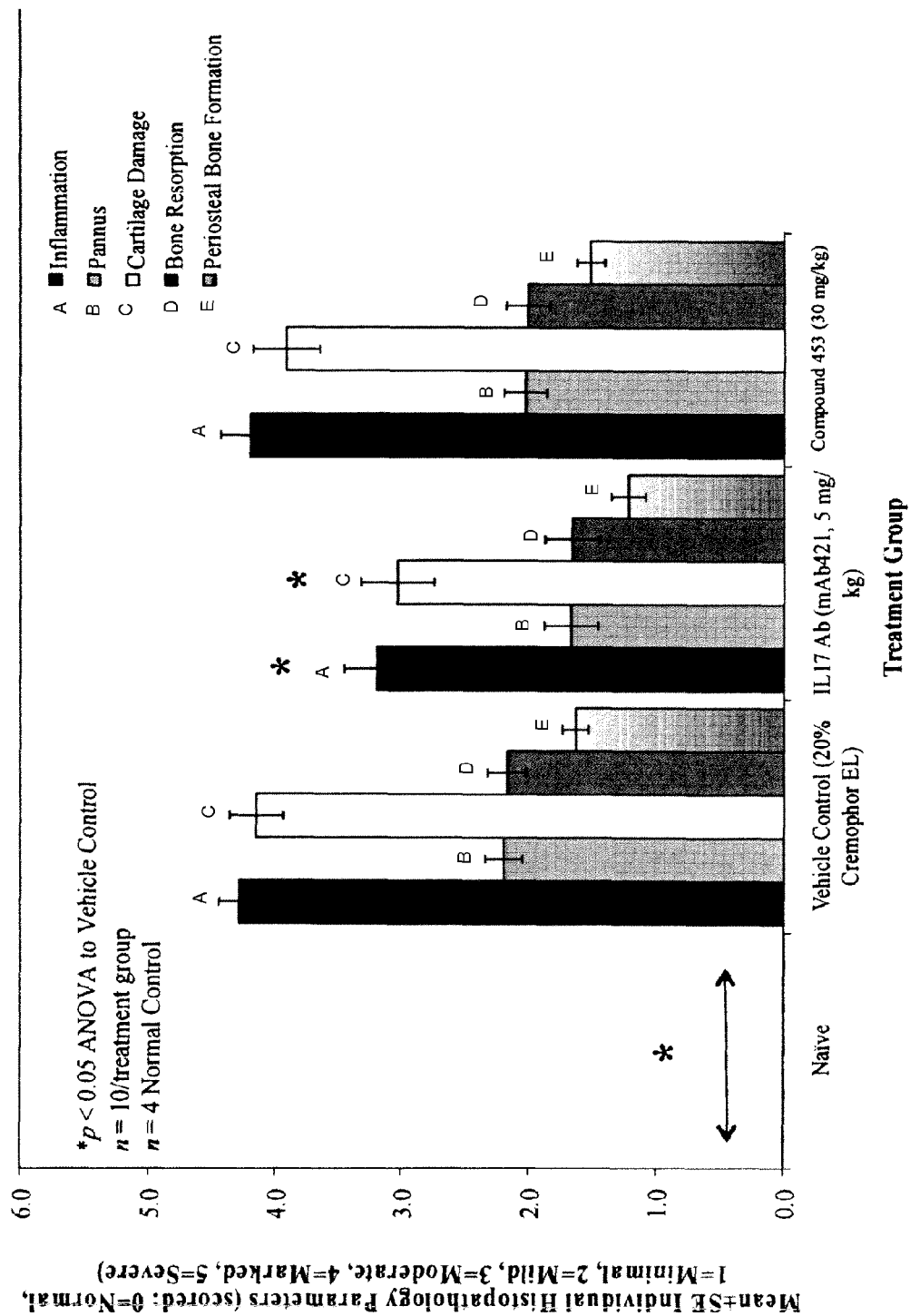


FIG. 7

FIG. 8



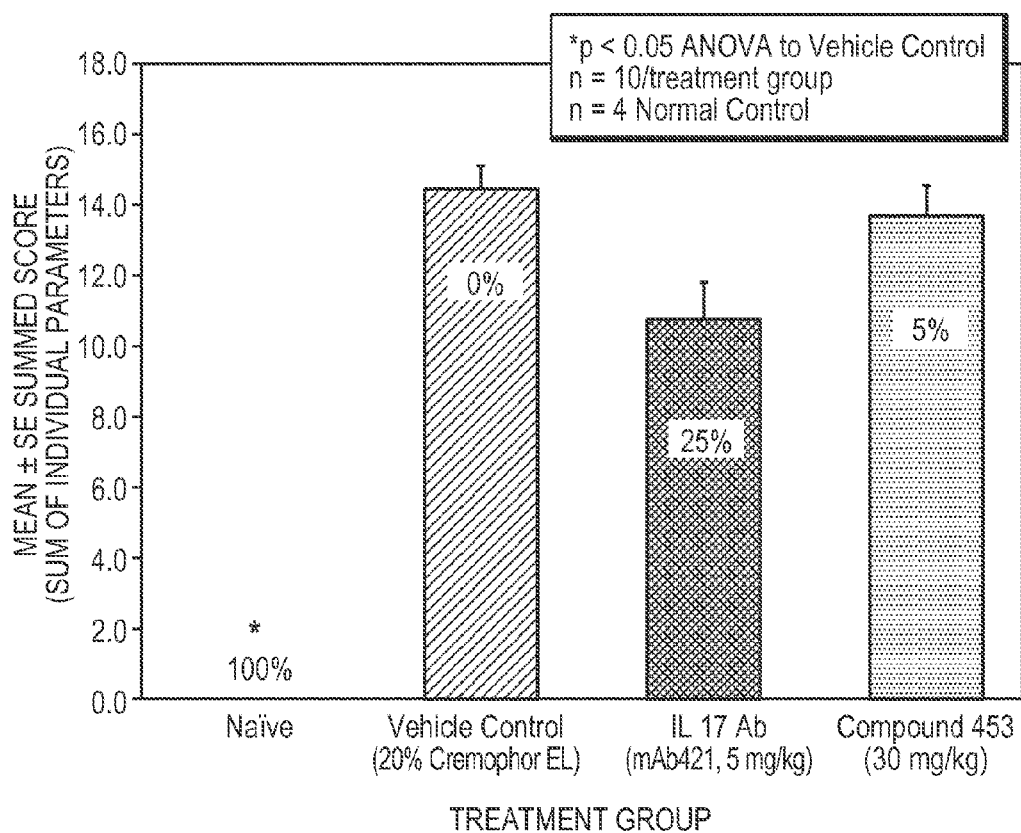
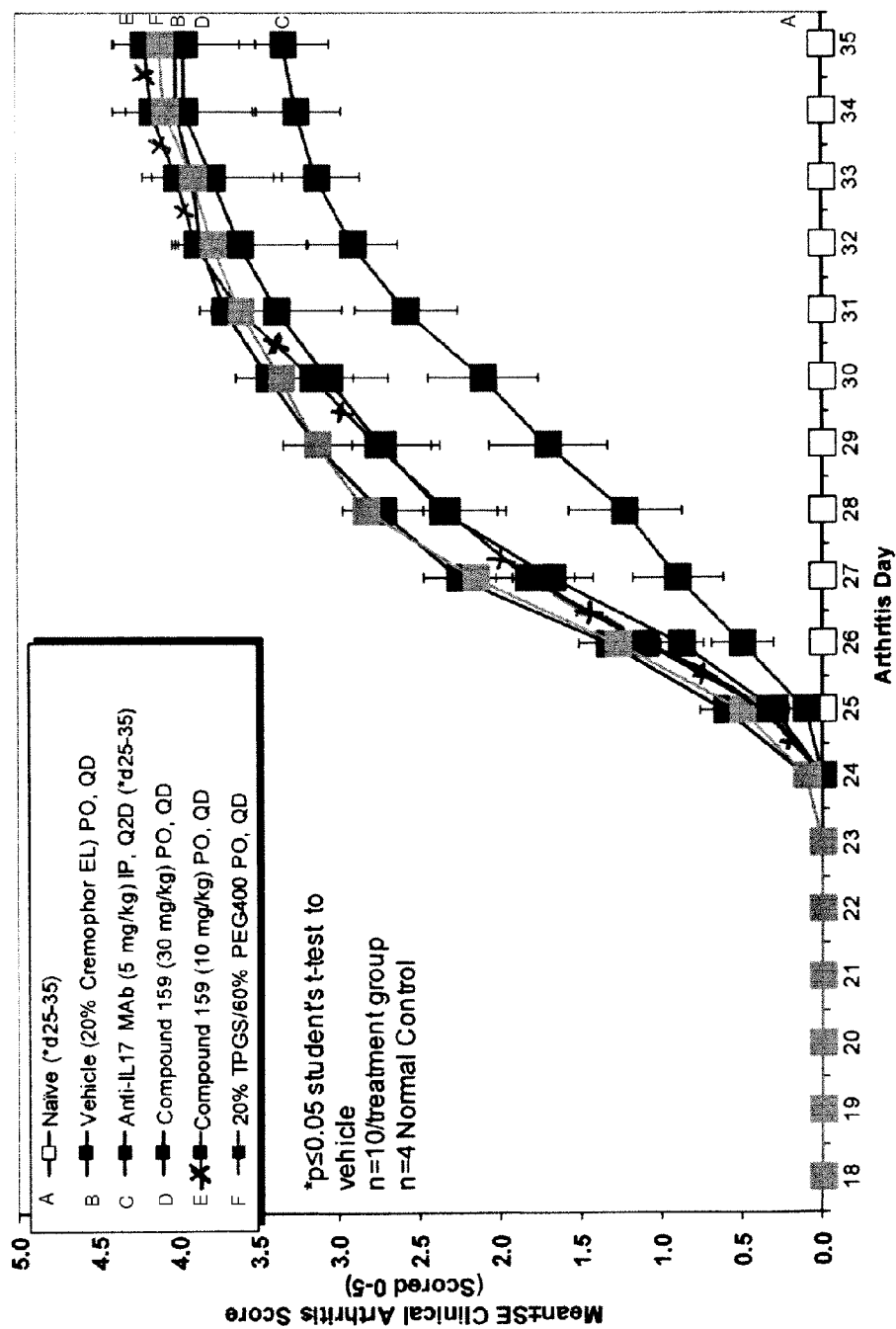


FIG. 9

FIG. 10



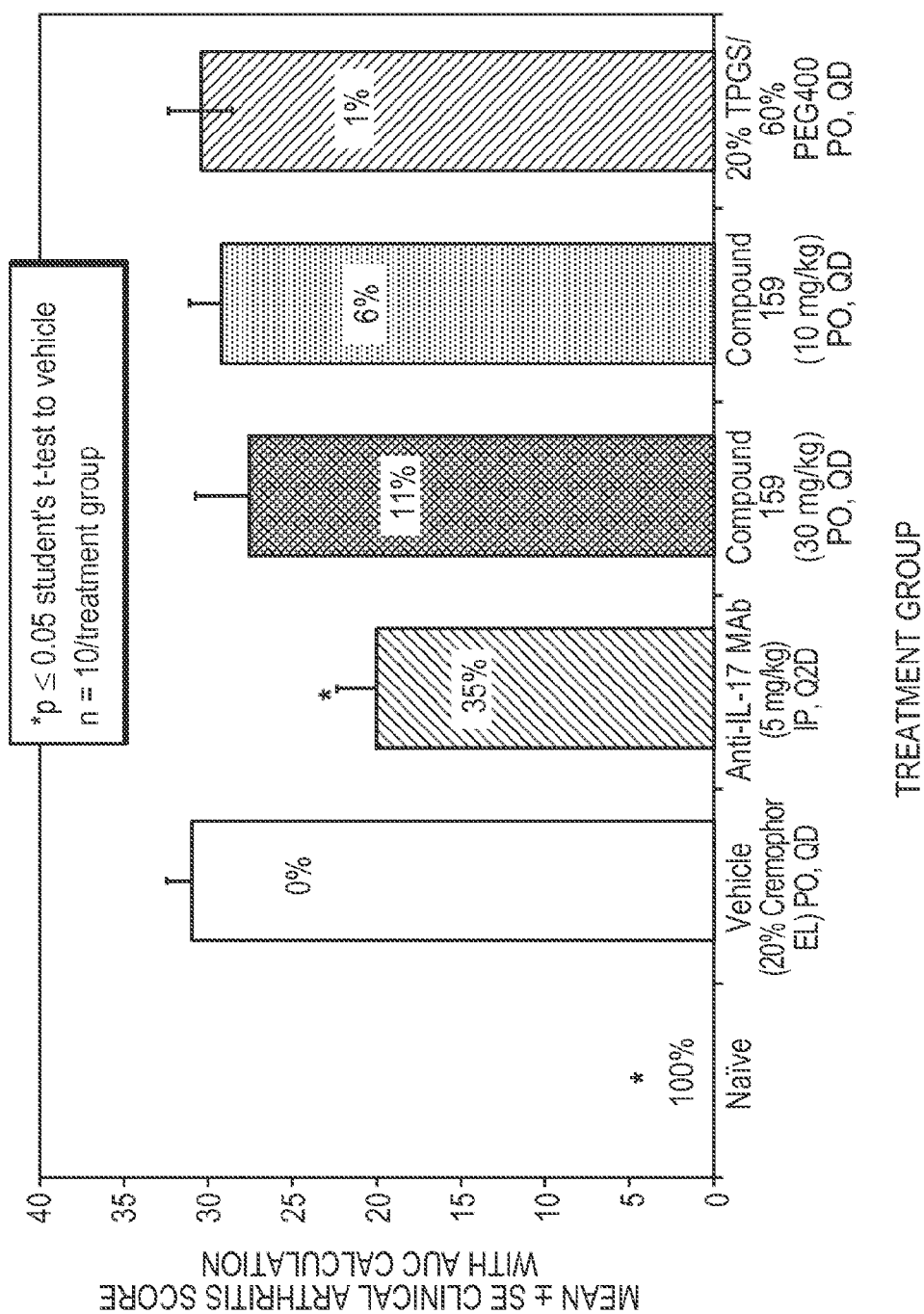


FIG. 11

Figure 12

Table 1. Exemplary Compounds of the Invention

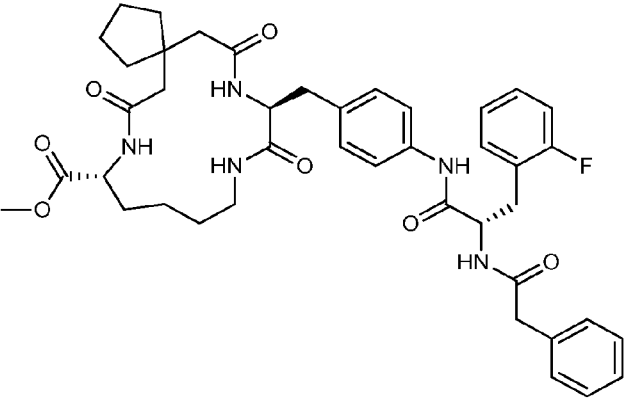
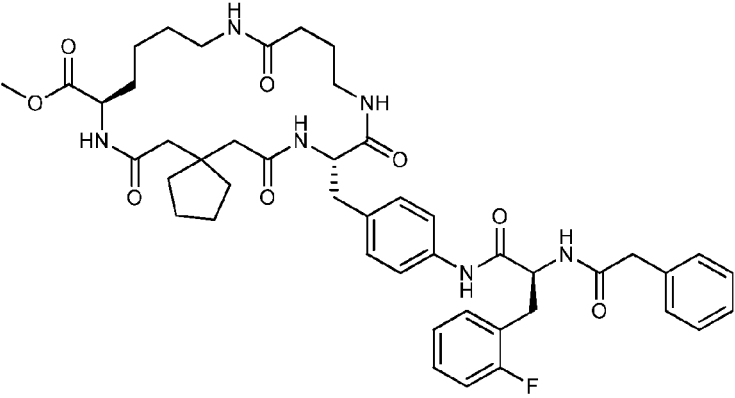
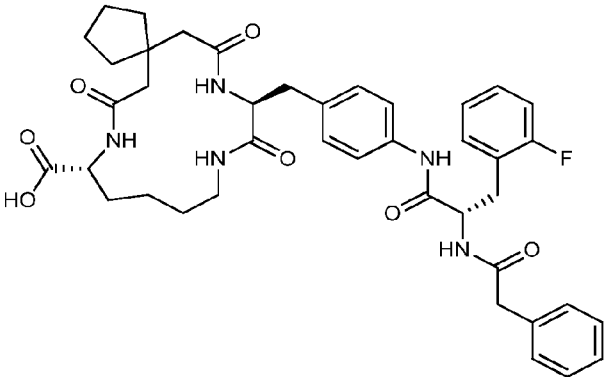
Compound No.	Structure
100	
101	
102	

FIG. 12-1

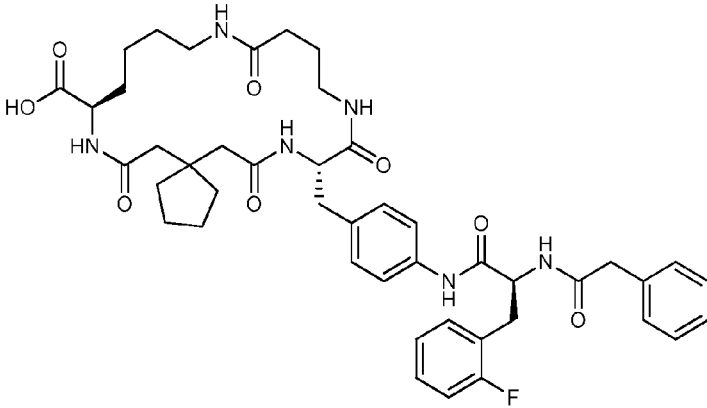
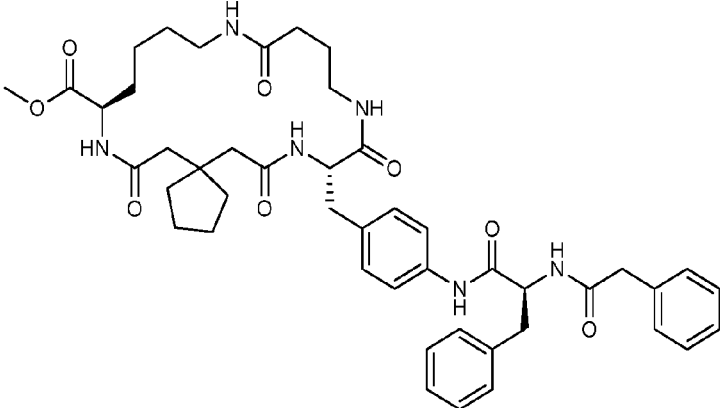
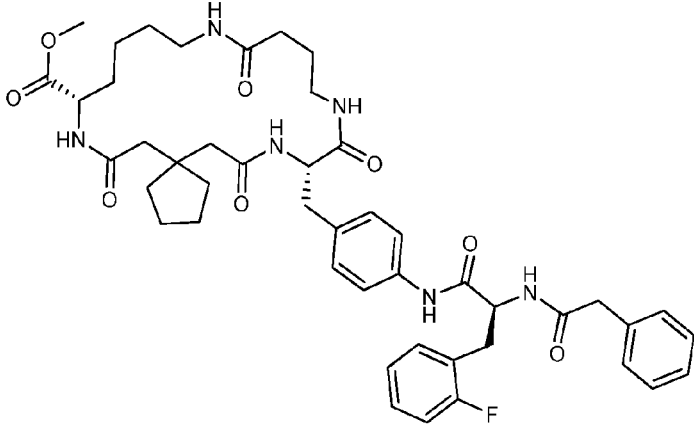
Compound No.	Structure
103	 <p>Chemical structure of Compound 103: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a carboxylic acid group (HO-C=O) and an amide linkage (NH-C=O). The other side of the ring is connected to a chain containing an amide linkage (NH-C=O) and a chiral center (indicated by a dashed bond). This chiral center is further connected to a phenyl ring, which is linked to another amide group (NH-C=O). This amide group is connected to a chiral center (indicated by a solid wedge bond), which is further connected to a benzamide group (NH-C(=O)-CH2-C6H5).</p>
104	 <p>Chemical structure of Compound 104: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a methyl ester group (CH3O-C=O) and an amide linkage (NH-C=O). The other side of the ring is connected to a chain containing an amide linkage (NH-C=O) and a chiral center (indicated by a dashed bond). This chiral center is further connected to a phenyl ring, which is linked to another amide group (NH-C=O). This amide group is connected to a chiral center (indicated by a solid wedge bond), which is further connected to a benzamide group (NH-C(=O)-CH2-C6H5).</p>
105	 <p>Chemical structure of Compound 105: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a methyl ester group (CH3O-C=O) and an amide linkage (NH-C=O). The other side of the ring is connected to a chain containing an amide linkage (NH-C=O) and a chiral center (indicated by a dashed bond). This chiral center is further connected to a phenyl ring, which is linked to another amide group (NH-C=O). This amide group is connected to a chiral center (indicated by a solid wedge bond), which is further connected to a benzamide group (NH-C(=O)-CH2-C6H5).</p>

FIG. 12-2

Compound No.	Structure
106	
107	
108	

FIG. 12-3

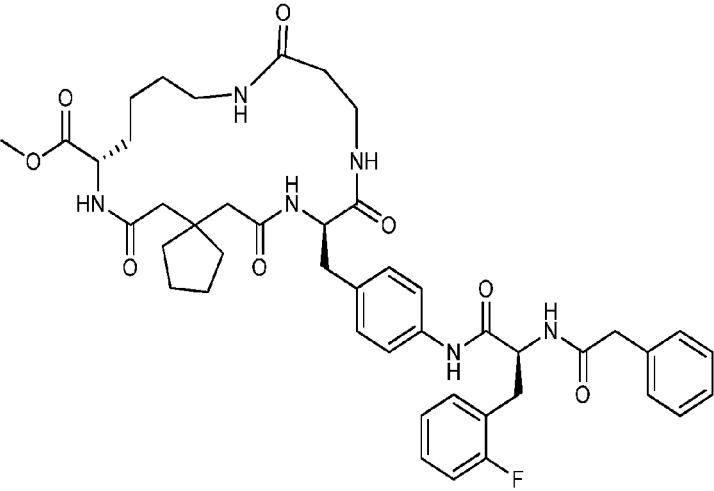
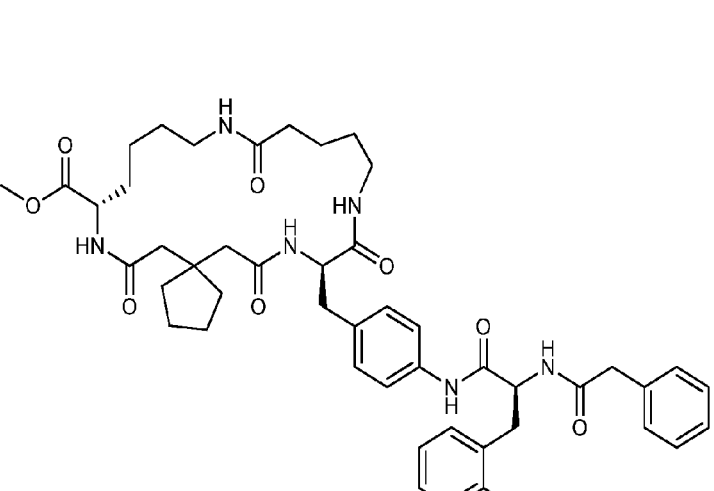
Compound No.	Structure
109	 <p>Chemical structure of Compound 109. The molecule features a central cyclopentane ring substituted with two amide groups. One amide is part of a side chain containing a methyl ester, a chiral center with a dashed bond, and a long amide linker. The other amide is part of a side chain containing a chiral center with a wedged bond, a benzyl group, and a 2-fluorophenyl group. The 2-fluorophenyl group is further substituted with a chiral center and a benzyl group, which is in turn substituted with a benzamide group.</p>
110	 <p>Chemical structure of Compound 110. This structure is identical to Compound 109, showing a cyclopentane core with two amide-linked side chains. One side chain includes a methyl ester, a chiral center with a dashed bond, and a long amide linker. The other side chain includes a chiral center with a wedged bond, a benzyl group, and a 2-fluorophenyl group, which is further substituted with a chiral center and a benzyl group, leading to a benzamide group.</p>

FIG. 12-4

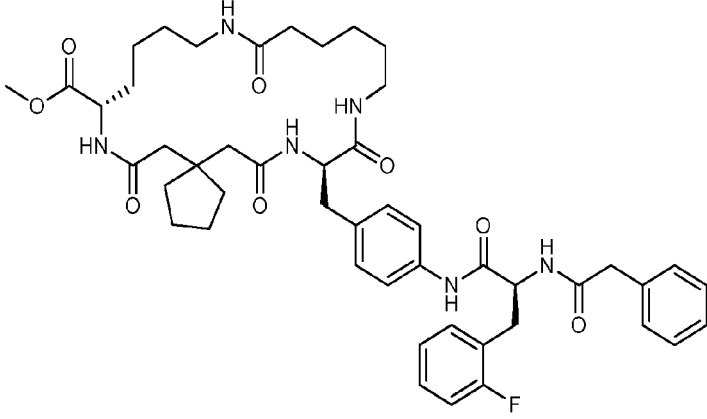
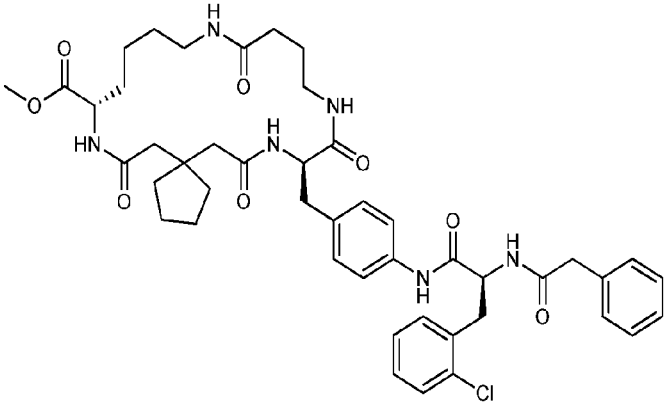
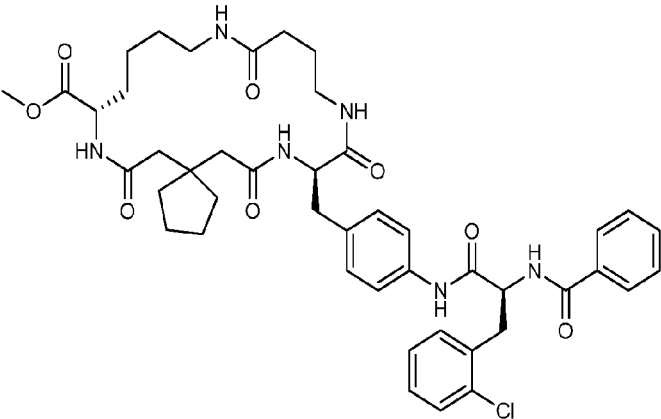
Compound No.	Structure
111	 <p>Chemical structure of Compound 111: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methyl ester group and a long alkyl chain. The other amide group is part of a chain that includes a benzamide group and a benzyl group. The benzyl group is further substituted with a fluorine atom.</p>
112	 <p>Chemical structure of Compound 112: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methyl ester group and a long alkyl chain. The other amide group is part of a chain that includes a benzamide group and a benzyl group. The benzyl group is further substituted with a chlorine atom.</p>
113	 <p>Chemical structure of Compound 113: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methyl ester group and a long alkyl chain. The other amide group is part of a chain that includes a benzamide group and a benzyl group. The benzyl group is further substituted with a chlorine atom.</p>

FIG. 12-5

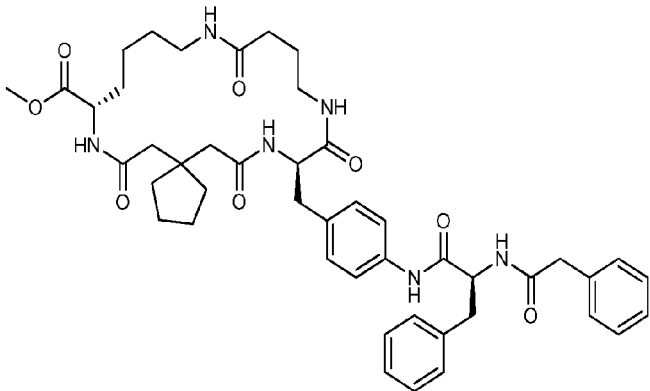
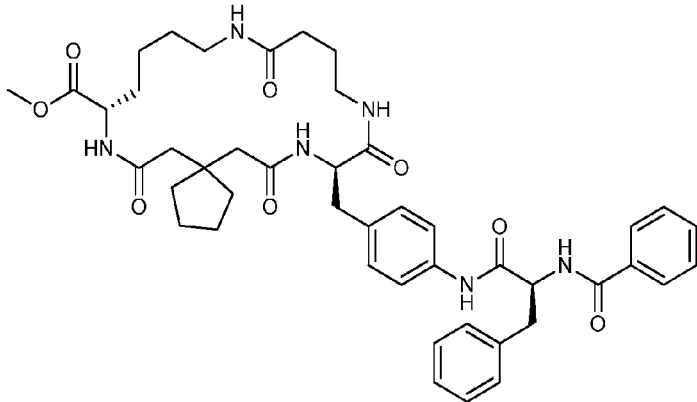
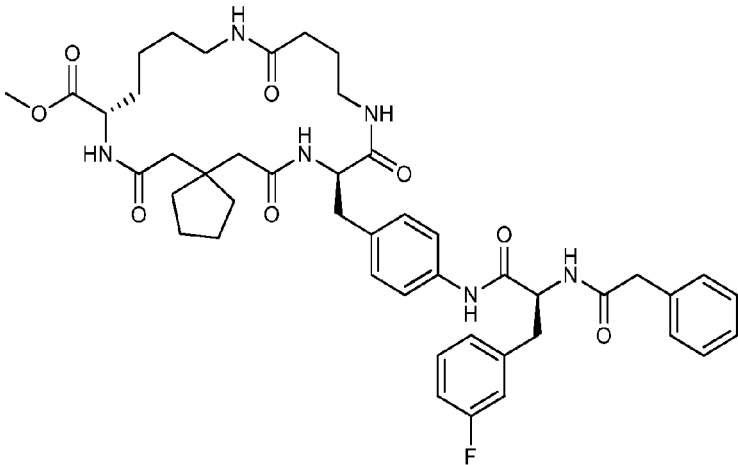
Compound No.	Structure
114	 <p>Chemical structure of compound 114: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a methyl ester group (CH₃COO-), a chiral center with a dashed bond, and an amide group (NH-CO-). Another carbon of the cyclopentane is part of a chain containing an amide group (NH-CO-), a chiral center with a solid bond, and a benzyl group (CH₂-C₆H₅). The benzyl group is further substituted with a 4-phenyl-2-phenyl-1,3-dioxane-5-carboxamide moiety, which is in turn substituted with a 2-phenylacetamide group.</p>
115	 <p>Chemical structure of compound 115: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a methyl ester group (CH₃COO-), a chiral center with a dashed bond, and an amide group (NH-CO-). Another carbon of the cyclopentane is part of a chain containing an amide group (NH-CO-), a chiral center with a solid bond, and a benzyl group (CH₂-C₆H₅). The benzyl group is further substituted with a 4-phenyl-2-phenyl-1,3-dioxane-5-carboxamide moiety, which is in turn substituted with a benzamide group (NH-CO-C₆H₅).</p>
116	 <p>Chemical structure of compound 116: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a methyl ester group (CH₃COO-), a chiral center with a dashed bond, and an amide group (NH-CO-). Another carbon of the cyclopentane is part of a chain containing an amide group (NH-CO-), a chiral center with a solid bond, and a benzyl group (CH₂-C₆H₅). The benzyl group is further substituted with a 4-(4-fluorophenyl)-2-(4-fluorophenyl)-1,3-dioxane-5-carboxamide moiety, which is in turn substituted with a 2-phenylacetamide group.</p>

FIG. 12-6

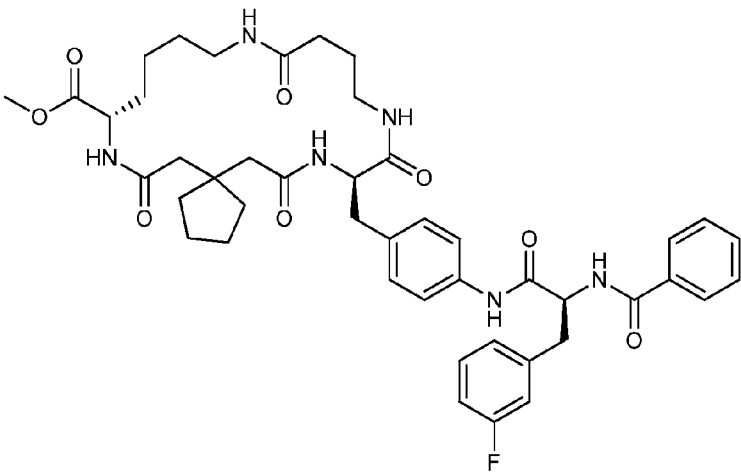
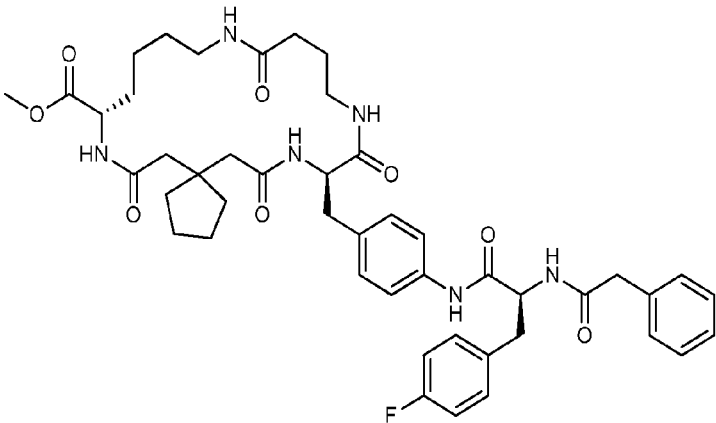
Compound No.	Structure
117	 <p>Chemical structure of Compound 117: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with a methyl ester group (CH₃COO-) and a side chain containing a secondary amide (NH) and a tertiary amide (N). The side chain is further substituted with a benzyl group (CH₂Ph) and a 4-fluorophenyl group (C₆H₄F). The molecule also contains a 4-phenylamino group (NHPh) and a 4-fluorophenyl group (C₆H₄F).</p>
118	 <p>Chemical structure of Compound 118: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with a methyl ester group (CH₃COO-) and a side chain containing a secondary amide (NH) and a tertiary amide (N). The side chain is further substituted with a benzyl group (CH₂Ph) and a 4-fluorophenyl group (C₆H₄F). The molecule also contains a 4-phenylamino group (NHPh) and a 4-fluorophenyl group (C₆H₄F).</p>

FIG. 12-7

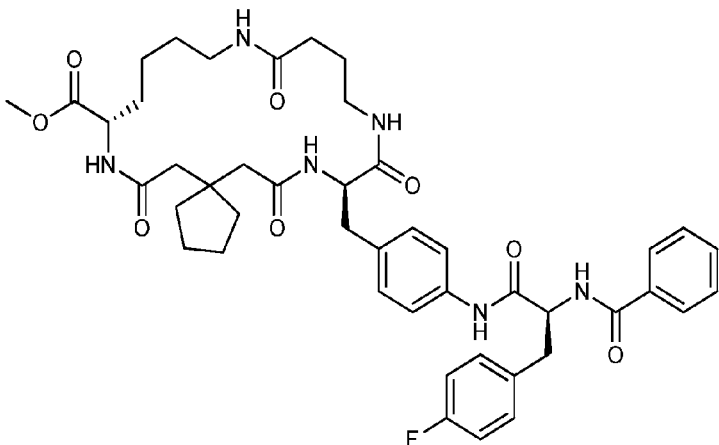
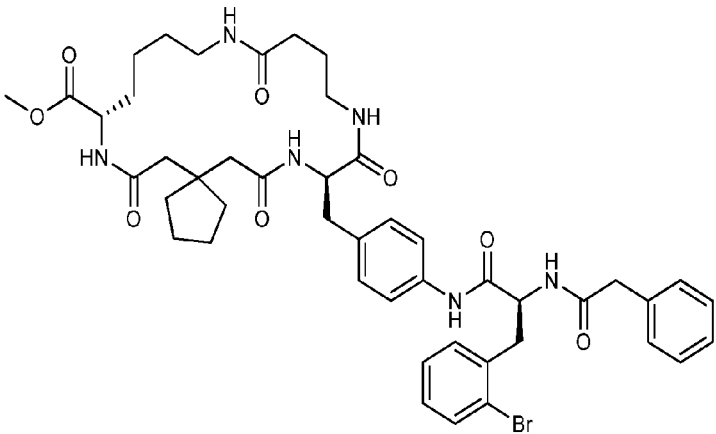
Compound No.	Structure
119	 <p>Chemical structure of Compound 119. It features a central cyclopentane ring substituted with two amide groups. One amide is part of a side chain containing a methyl ester, a 4-fluorophenyl group, and a benzamide moiety. The other amide is part of a side chain containing a 4-phenyl group and a benzamide moiety. The two side chains are connected via a long amide linkage.</p>
120	 <p>Chemical structure of Compound 120. It is similar to Compound 119, but the 4-fluorophenyl group is replaced by a 3-bromophenyl group.</p>

FIG. 12-8

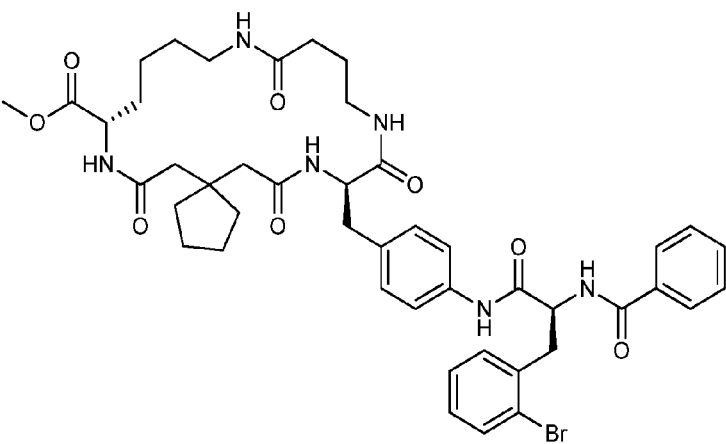
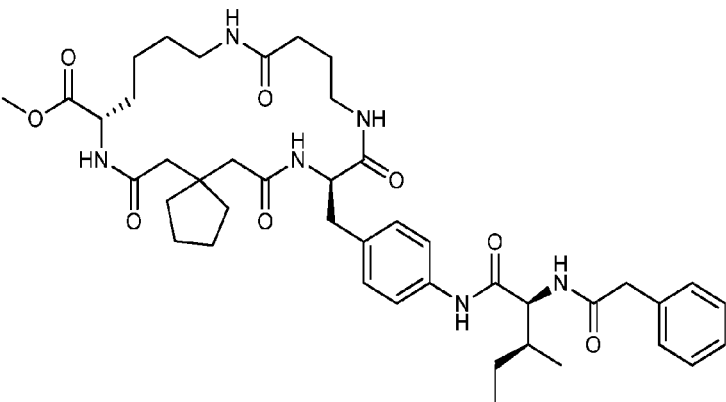
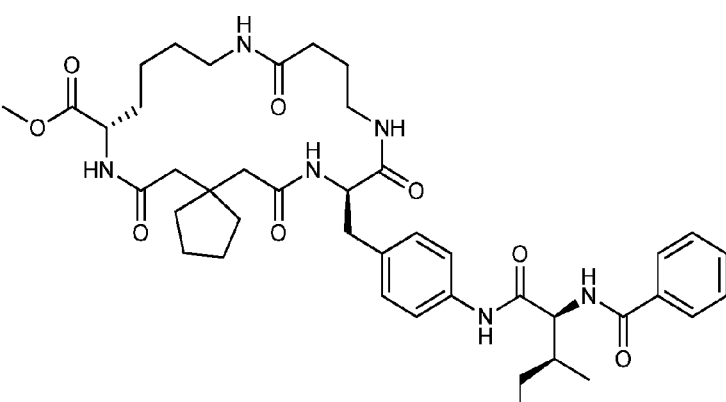
Compound No.	Structure
121	 <p>Chemical structure of Compound 121: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a methyl ester group (CH₃COO-), a chiral center (indicated by a dashed bond), and an amide group (NH-CO-). The other side of the ring is connected to a chain containing an amide group (NH-CO-), a chiral center (indicated by a solid wedge bond), and a phenyl ring. The phenyl ring is further substituted with a bromine atom (Br) and a side chain containing an amide group (NH-CO-) and a benzoyl group (C₆H₅CO-).</p>
122	 <p>Chemical structure of Compound 122: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a methyl ester group (CH₃COO-), a chiral center (indicated by a dashed bond), and an amide group (NH-CO-). The other side of the ring is connected to a chain containing an amide group (NH-CO-), a chiral center (indicated by a solid wedge bond), and a phenyl ring. The phenyl ring is further substituted with a side chain containing an amide group (NH-CO-) and a benzoyl group (C₆H₅CO-).</p>
123	 <p>Chemical structure of Compound 123: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a methyl ester group (CH₃COO-), a chiral center (indicated by a dashed bond), and an amide group (NH-CO-). The other side of the ring is connected to a chain containing an amide group (NH-CO-), a chiral center (indicated by a solid wedge bond), and a phenyl ring. The phenyl ring is further substituted with a side chain containing an amide group (NH-CO-) and a benzoyl group (C₆H₅CO-).</p>

FIG. 12-9

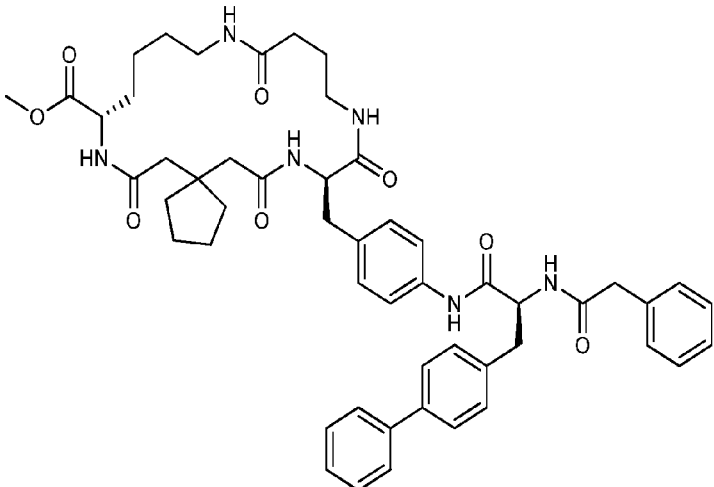
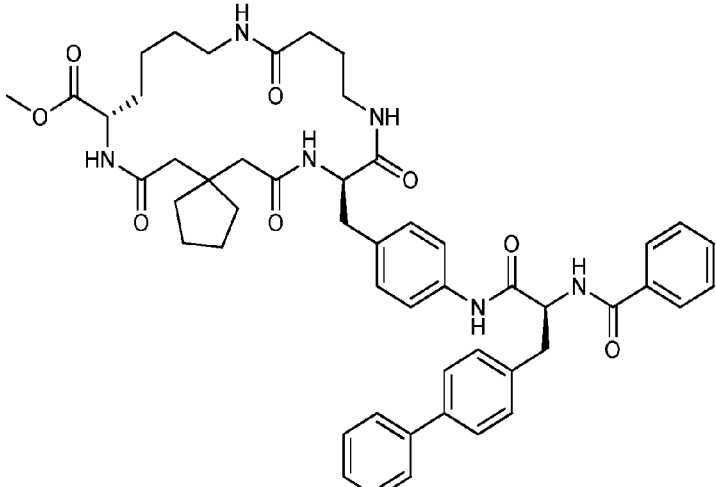
Compound No.	Structure
124	 <p>Chemical structure of Compound 124. It features a central cyclopentane ring substituted with two amide groups. One amide is part of a side chain containing a methyl ester, a long alkyl chain with an internal amide, and a terminal amide. The other amide is part of a side chain containing a long alkyl chain with an internal amide and a terminal amide. The side chains are further substituted with a biphenyl group and a benzamide group.</p>
125	 <p>Chemical structure of Compound 125. It is similar to Compound 124, but the side chain containing the biphenyl group is substituted with a benzamide group instead of a benzamide group.</p>

FIG. 12-10

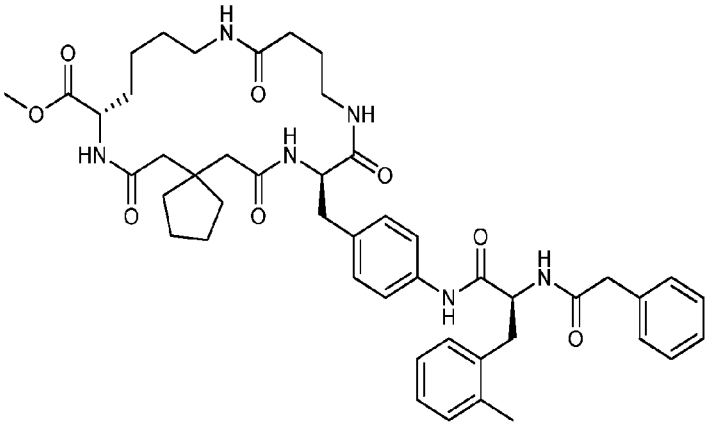
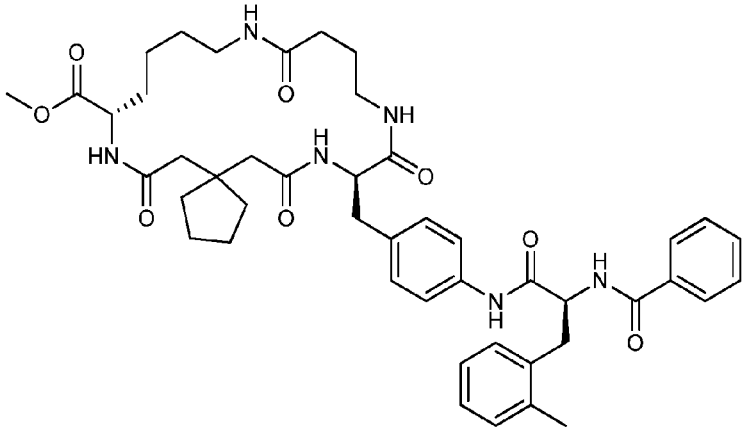
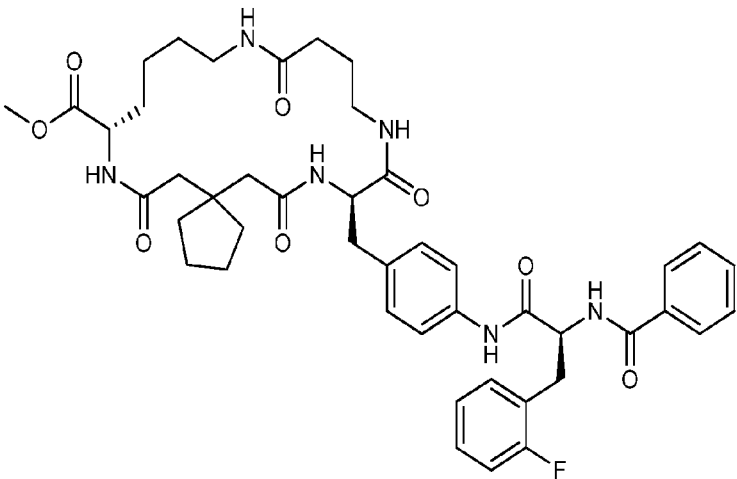
Compound No.	Structure
126	 <p>Chemical structure of Compound 126: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with a methyl ester group (CH₃COO-) and a side chain containing a secondary amide (NH) and a tertiary amide (N). The side chain is further substituted with a benzyl group (CH₂Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O). The molecule also contains a phenyl ring (Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O).</p>
127	 <p>Chemical structure of Compound 127: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with a methyl ester group (CH₃COO-) and a side chain containing a secondary amide (NH) and a tertiary amide (N). The side chain is further substituted with a benzyl group (CH₂Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O). The molecule also contains a phenyl ring (Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O).</p>
128	 <p>Chemical structure of Compound 128: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with a methyl ester group (CH₃COO-) and a side chain containing a secondary amide (NH) and a tertiary amide (N). The side chain is further substituted with a benzyl group (CH₂Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O). The molecule also contains a phenyl ring (Ph) and a benzyl group (CH₂Ph) attached to a carbonyl group (C=O).</p>

FIG. 12-11

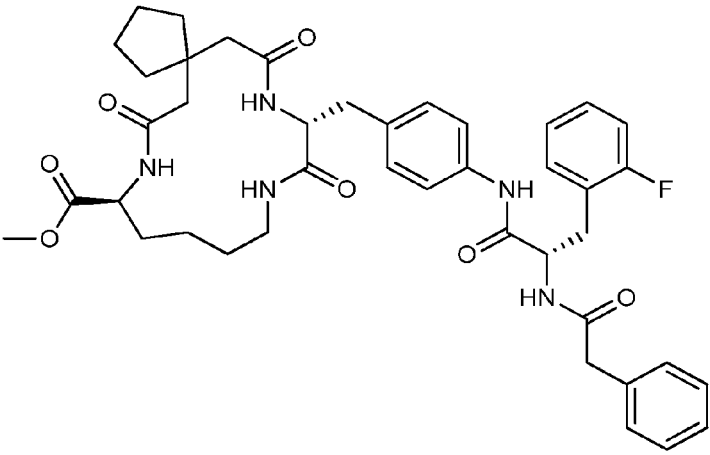
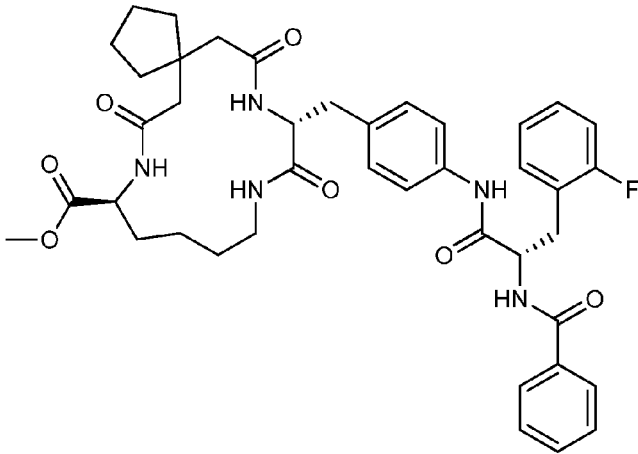
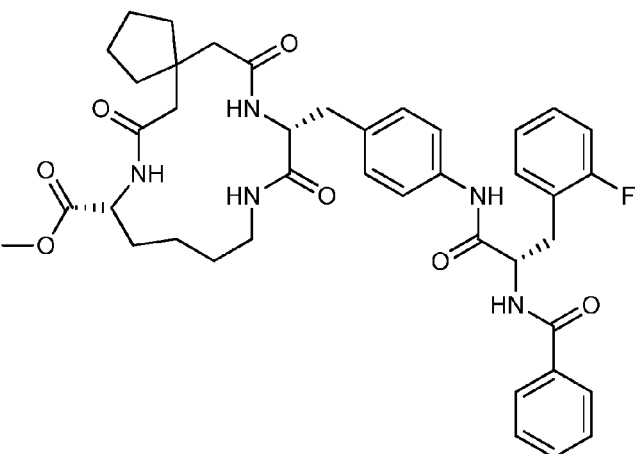
Compound No.	Structure
129	 <p>Chemical structure of Compound 129: A macrocyclic molecule featuring a 15-membered ring with two amide bonds and a methyl ester group. The ring is substituted with a cyclopentyl group, a p-phenylene group, and a 2-fluorophenyl group. The side chain includes a benzyl group and a 2-fluorophenyl group.</p>
130	 <p>Chemical structure of Compound 130: A macrocyclic molecule featuring a 15-membered ring with two amide bonds and a methyl ester group. The ring is substituted with a cyclopentyl group, a p-phenylene group, and a 2-fluorophenyl group. The side chain includes a benzyl group and a 2-fluorophenyl group.</p>
131	 <p>Chemical structure of Compound 131: A macrocyclic molecule featuring a 15-membered ring with two amide bonds and a methyl ester group. The ring is substituted with a cyclopentyl group, a p-phenylene group, and a 2-fluorophenyl group. The side chain includes a benzyl group and a 2-fluorophenyl group.</p>

FIG. 12-12

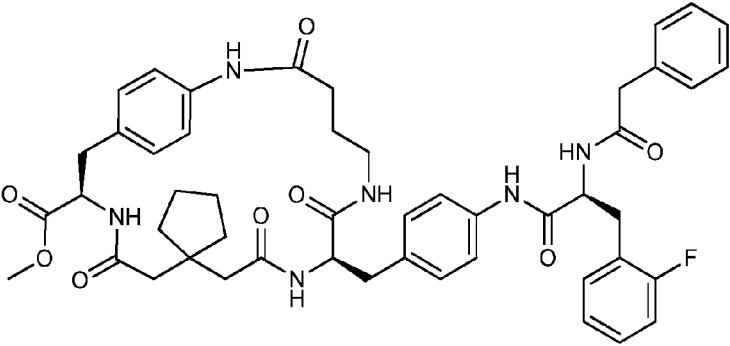
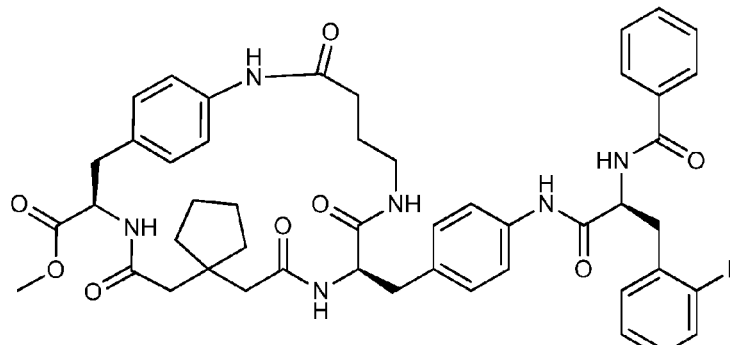
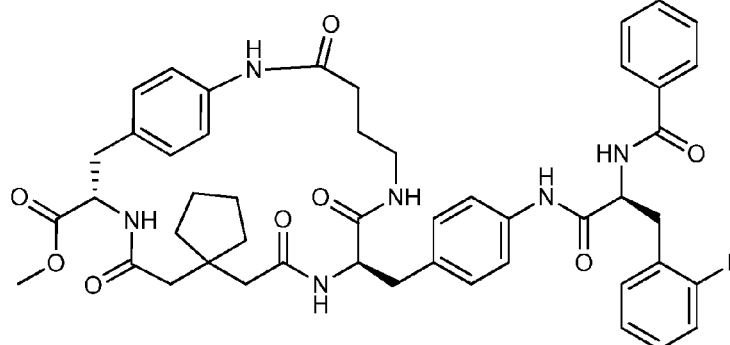
Compound No.	Structure
132	 <p>Chemical structure of Compound 132: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. Another carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. The molecule includes several amide linkages, a methyl ester group, and a 2-fluorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>
133	 <p>Chemical structure of Compound 133: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. Another carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. The molecule includes several amide linkages, a methyl ester group, and a 2-fluorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>
134	 <p>Chemical structure of Compound 134: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. Another carbon of the cyclopentane is part of a five-membered lactam ring (pyrrolidine) fused to a benzene ring. The molecule includes several amide linkages, a methyl ester group, and a 2-fluorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-13

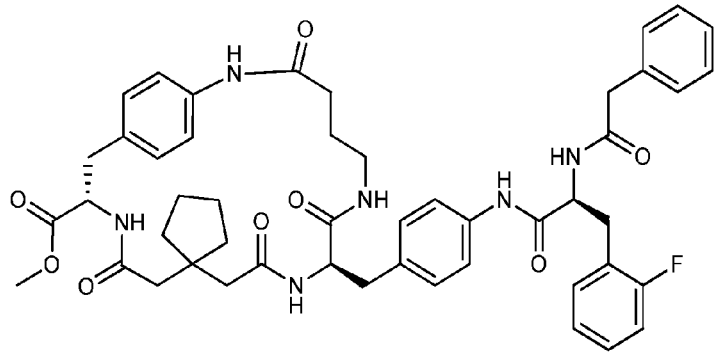
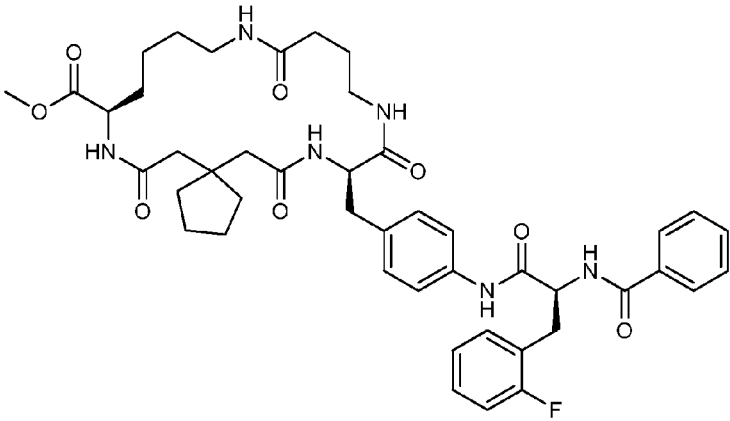
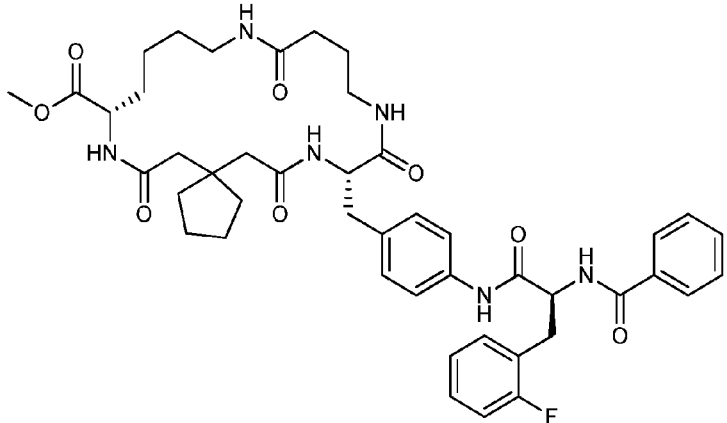
Compound No.	Structure
135	 <p>Chemical structure of Compound 135: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a benzamide group (NH-C(=O)-CH2-CH2-Ph) and a methyl ester group (CO2Me). The other side of the ring is connected to a chain containing an amide group (NH-C(=O)-CH2-CH2-Ph) and a 2-fluorophenyl group (Ph-F). The two chains are linked via a central amide bond (NH-C(=O)-CH2-CH2-Ph).</p>
136	 <p>Chemical structure of Compound 136: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a benzamide group (NH-C(=O)-CH2-CH2-Ph) and a methyl ester group (CO2Me). The other side of the ring is connected to a chain containing an amide group (NH-C(=O)-CH2-CH2-Ph) and a 2-fluorophenyl group (Ph-F). The two chains are linked via a central amide bond (NH-C(=O)-CH2-CH2-Ph).</p>
137	 <p>Chemical structure of Compound 137: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a chain containing a benzamide group (NH-C(=O)-CH2-CH2-Ph) and a methyl ester group (CO2Me). The other side of the ring is connected to a chain containing an amide group (NH-C(=O)-CH2-CH2-Ph) and a 2-fluorophenyl group (Ph-F). The two chains are linked via a central amide bond (NH-C(=O)-CH2-CH2-Ph).</p>

FIG. 12-14

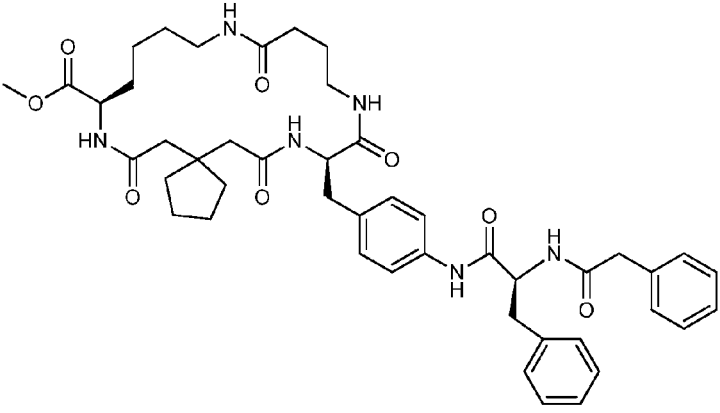
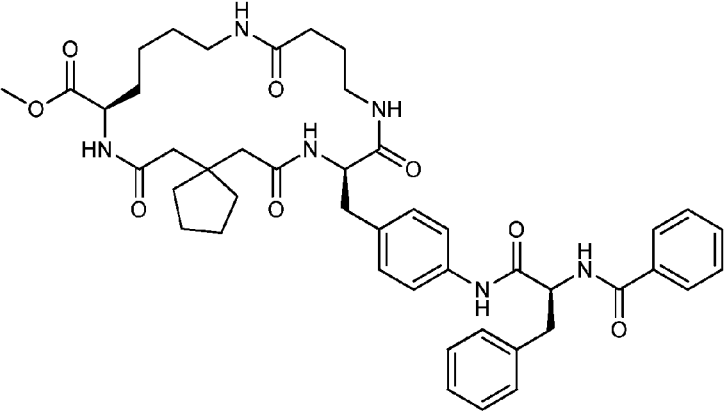
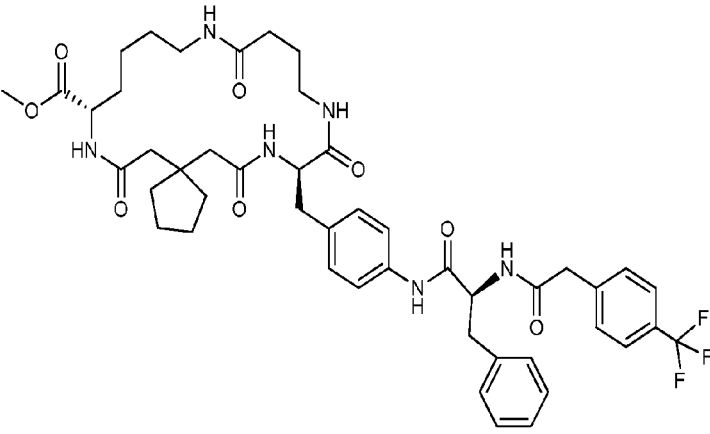
Compound No.	Structure
138	 <p>Chemical structure of Compound 138: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methoxycarbonyl group and a benzyl group. The other amide group is part of a chain that includes a benzyl group and a benzyl group. The molecule also contains several other amide and ester functional groups.</p>
139	 <p>Chemical structure of Compound 139: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methoxycarbonyl group and a benzyl group. The other amide group is part of a chain that includes a benzyl group and a benzyl group. The molecule also contains several other amide and ester functional groups.</p>
140	 <p>Chemical structure of Compound 140: A complex molecule featuring a central cyclopentane ring. The cyclopentane ring is substituted with two amide groups. One amide group is part of a chain that includes a methoxycarbonyl group and a benzyl group. The other amide group is part of a chain that includes a benzyl group and a benzyl group. The molecule also contains several other amide and ester functional groups.</p>

FIG. 12-15

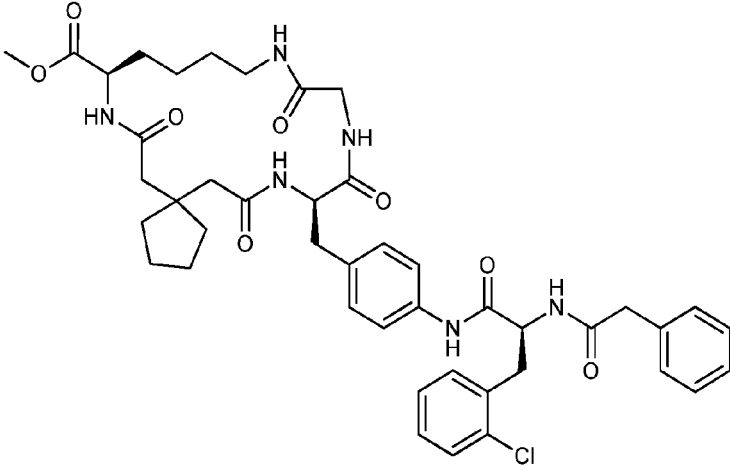
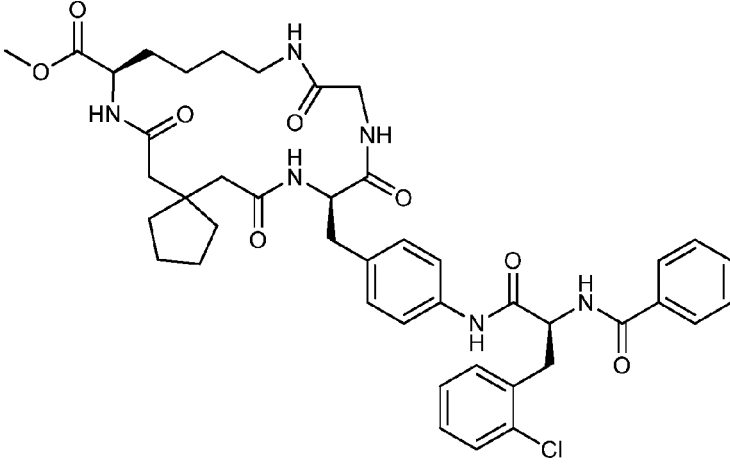
Compound No.	Structure
141	 <p>Chemical structure of Compound 141. It features a central bicyclic amide core (a cyclopentane ring fused to a five-membered amide ring). This core is substituted with a long chain containing a methyl ester group, a secondary amide, and a tertiary amide. The tertiary amide is further substituted with a 4-phenylphenyl group and a 2-chlorophenyl group. The 2-chlorophenyl group is also substituted with a benzyl group and a benzamide group.</p>
142	 <p>Chemical structure of Compound 142. It features a central bicyclic amide core (a cyclopentane ring fused to a five-membered amide ring). This core is substituted with a long chain containing a methyl ester group, a secondary amide, and a tertiary amide. The tertiary amide is further substituted with a 4-phenylphenyl group and a 2-chlorophenyl group. The 2-chlorophenyl group is also substituted with a benzyl group and a benzamide group.</p>

FIG. 12-16

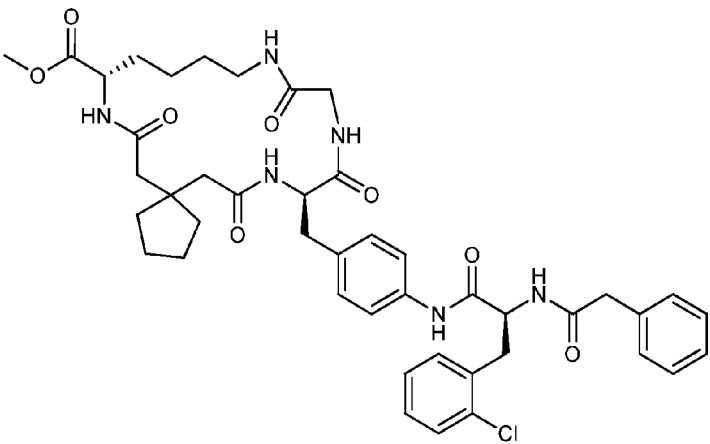
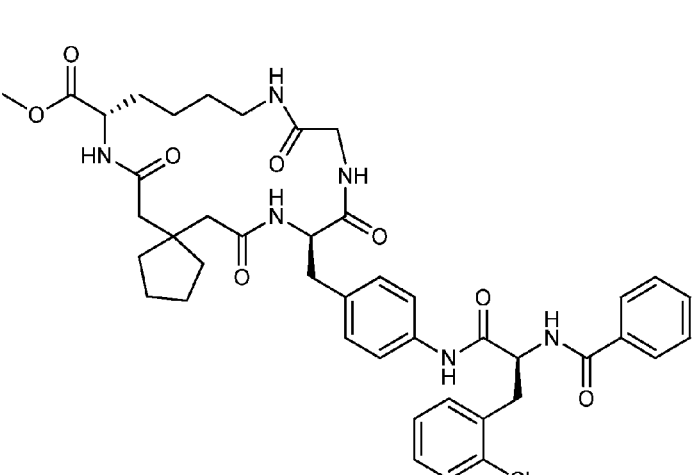
Compound No.	Structure
143	 <p>Chemical structure of Compound 143: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) bearing a methoxycarbonyl group and a hydrogen atom. The right side features a 4-chlorophenyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) bearing a hydrogen atom and a benzoyl group. The central amide linkage connects the two sides.</p>
144	 <p>Chemical structure of Compound 144: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) bearing a methoxycarbonyl group and a hydrogen atom. The right side features a 4-chlorophenyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) bearing a hydrogen atom and a benzoyl group. The central amide linkage connects the two sides.</p>

FIG. 12-17

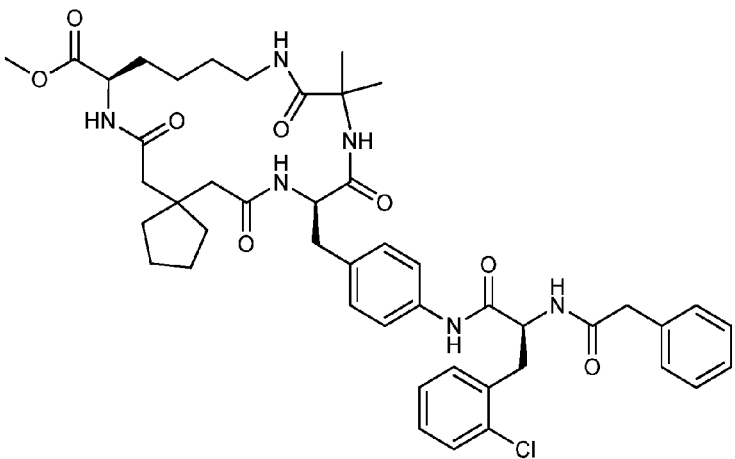
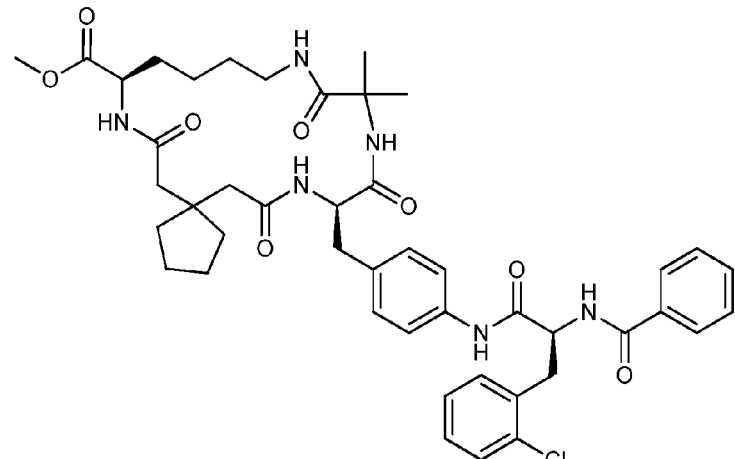
Compound No.	Structure
145	 <p>Chemical structure of Compound 145: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chain containing a methoxycarbonyl group and a secondary amide. The right side features a 2-chlorophenyl ring connected to a carbonyl group, which is further linked to a chain containing a benzamide group and a secondary amide. The structure is highly branched and contains multiple amide and carbonyl functional groups.</p>
146	 <p>Chemical structure of Compound 146: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chain containing a methoxycarbonyl group and a secondary amide. The right side features a 2-chlorophenyl ring connected to a carbonyl group, which is further linked to a chain containing a benzamide group and a secondary amide. The structure is highly branched and contains multiple amide and carbonyl functional groups.</p>

FIG. 12-18

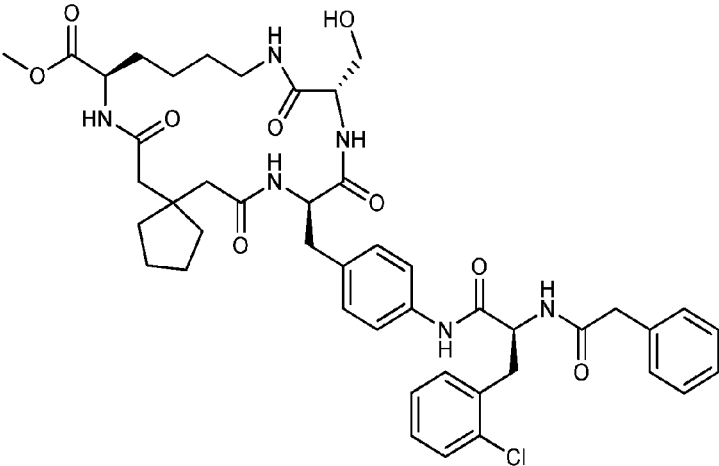
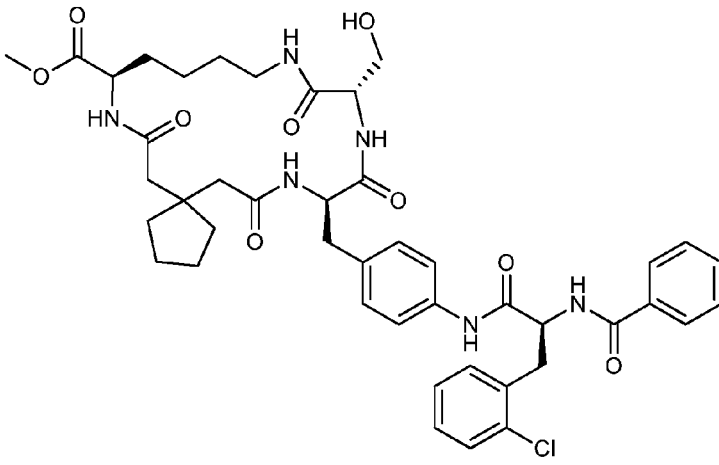
Compound No.	Structure
147	 <p>Chemical structure of Compound 147. It features a complex molecule with a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chain containing a methoxy group and a hydroxyl group. The right side includes a benzene ring with a chlorine substituent, connected to a carbonyl group, which is further linked to a chain containing a benzyl group and a hydroxyl group.</p>
148	 <p>Chemical structure of Compound 148. It is similar to Compound 147, but the right side of the molecule is modified, featuring a different arrangement of the benzene ring and the carbonyl group, resulting in a distinct chemical structure.</p>

FIG. 12-19

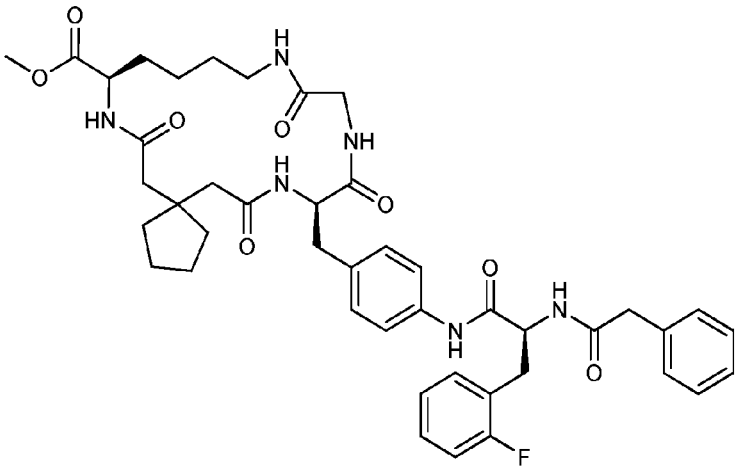
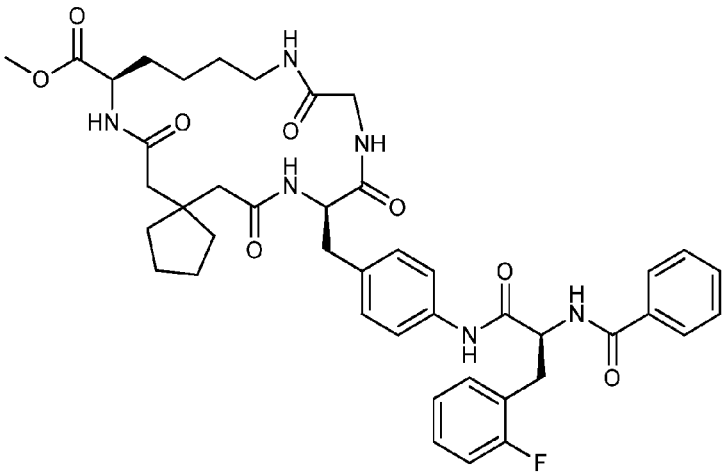
Compound No.	Structure
149	 <p>Chemical structure of Compound 149. It features a complex molecule with a central amide linkage. On the left, there is a cyclopentyl ring connected to a carbonyl group, which is part of a larger amide structure. This is linked to a long chain containing another amide and a methoxy group. On the right, there is a benzamide moiety with a fluorophenyl group and a benzyl group.</p>
150	 <p>Chemical structure of Compound 150. It is similar to Compound 149 but lacks the additional amide and methoxy group on the left side. It features a central amide linkage connecting a cyclopentyl ring to a benzamide moiety with a fluorophenyl group and a benzyl group.</p>

FIG. 12-20

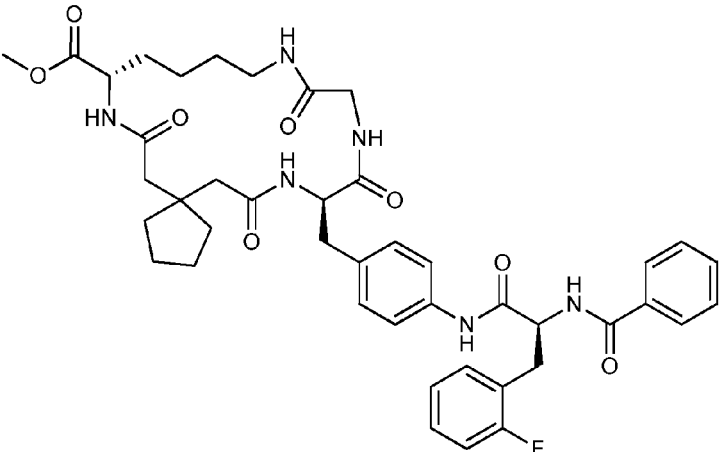
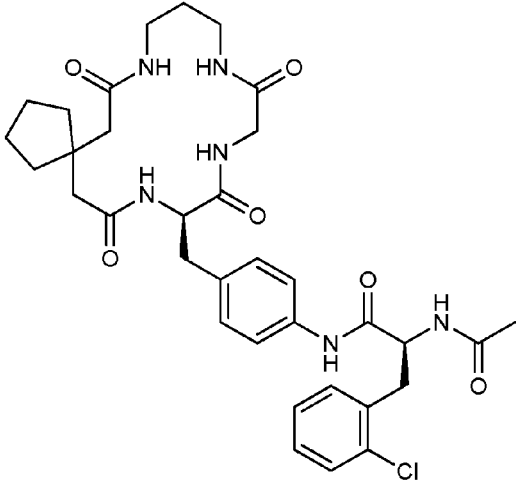
Compound No.	Structure
151	 <p>Chemical structure of Compound 151: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) and a methoxy group. The right side includes a benzamide moiety with a fluorophenyl substituent and a benzoyl group.</p>
152	 <p>Chemical structure of Compound 152: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a wedge bond) and a methoxy group. The right side includes a benzamide moiety with a chlorophenyl substituent and an acetamido group.</p>

FIG. 12-21

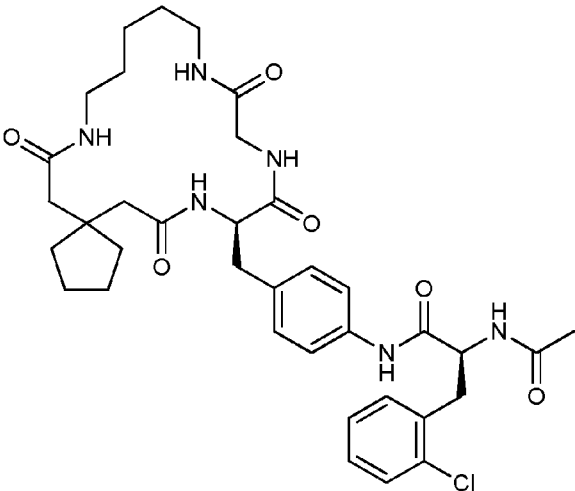
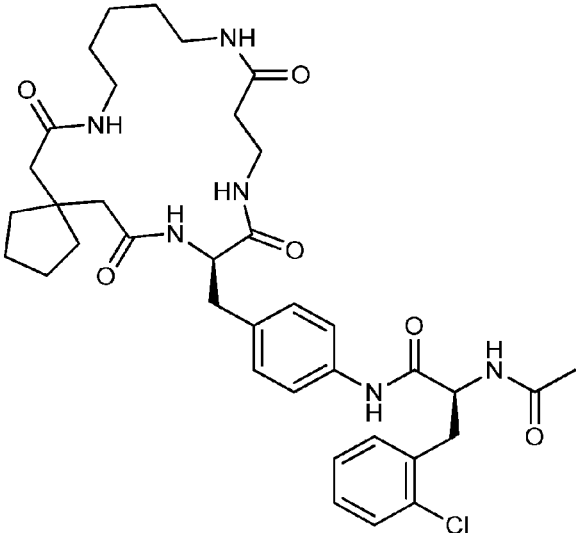
Compound No.	Structure
153	 <p>Chemical structure of Compound 153: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a long-chain amide. This amide is linked to a chiral center, which is further connected to a benzene ring. The benzene ring is substituted with a carbonyl group and a chiral center, which is linked to a benzene ring with a chlorine substituent. The molecule also includes a long-chain amide and a carbonyl group.</p>
154	 <p>Chemical structure of Compound 154: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a long-chain amide. This amide is linked to a chiral center, which is further connected to a benzene ring. The benzene ring is substituted with a carbonyl group and a chiral center, which is linked to a benzene ring with a chlorine substituent. The molecule also includes a long-chain amide and a carbonyl group.</p>

FIG. 12-22

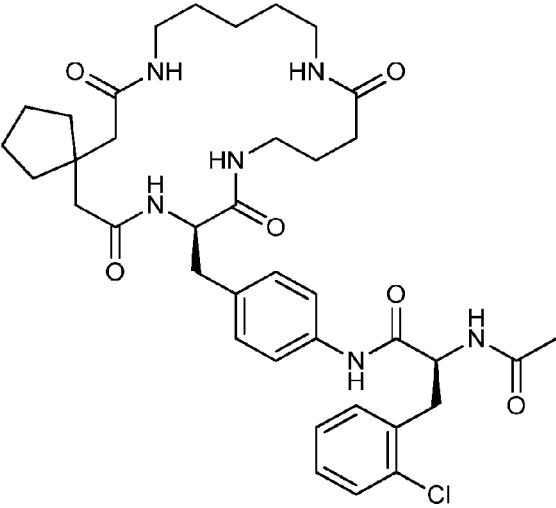
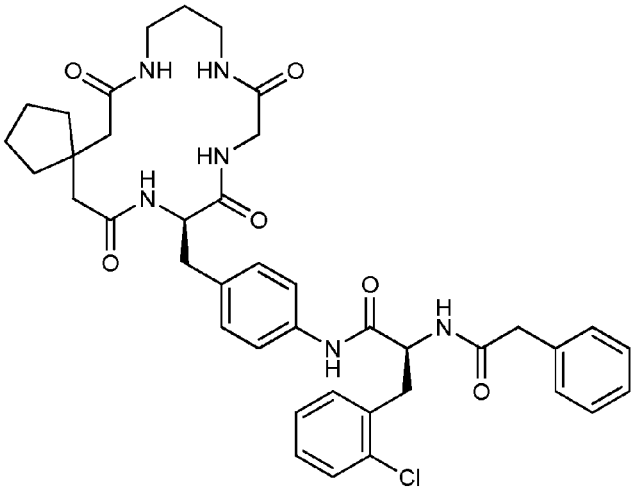
Compound No.	Structure
155	 <p>Chemical structure of Compound 155: A complex molecule featuring a cyclopentyl group attached to a chain containing two amide bonds and a 1,4-bis(benzyl)benzene moiety. The structure includes a 2-chlorophenyl ring and a 2-chlorophenyl ring.</p>
156	 <p>Chemical structure of Compound 156: A complex molecule featuring a cyclopentyl group attached to a chain containing two amide bonds and a 1,4-bis(benzyl)benzene moiety. The structure includes a 2-chlorophenyl ring and a 2-chlorophenyl ring.</p>

FIG. 12-23

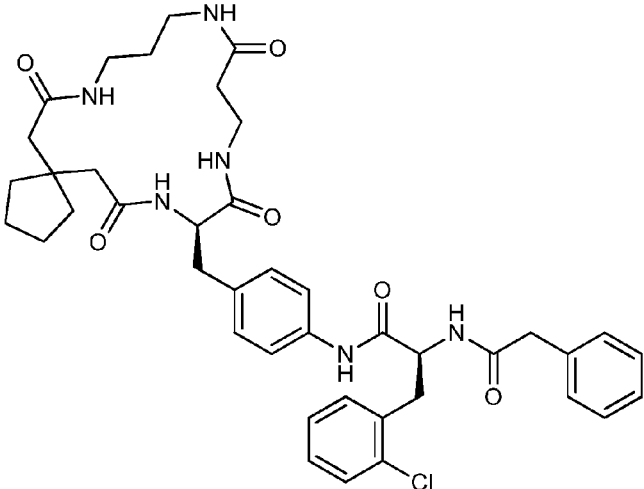
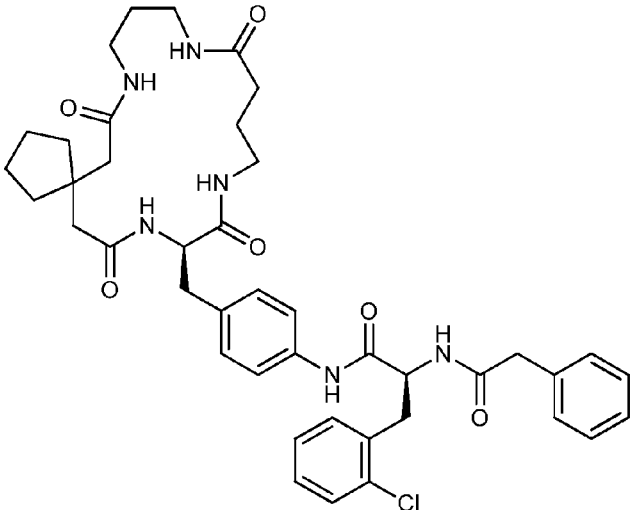
Compound No.	Structure
157	 <p>Chemical structure of Compound 157: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group. This is linked via a chiral center to a benzyl group, which is further connected to a 2-chlorophenyl ring. The 2-chlorophenyl ring is part of a larger system that includes a benzyl group and a carboxamide group, which is in turn linked to a benzyl group and a carboxamide group.</p>
158	 <p>Chemical structure of Compound 158: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group. This is linked via a chiral center to a benzyl group, which is further connected to a 2-chlorophenyl ring. The 2-chlorophenyl ring is part of a larger system that includes a benzyl group and a carboxamide group, which is in turn linked to a benzyl group and a carboxamide group.</p>

FIG. 12-24

Compound No.	Structure
159	
160	

FIG. 12-25

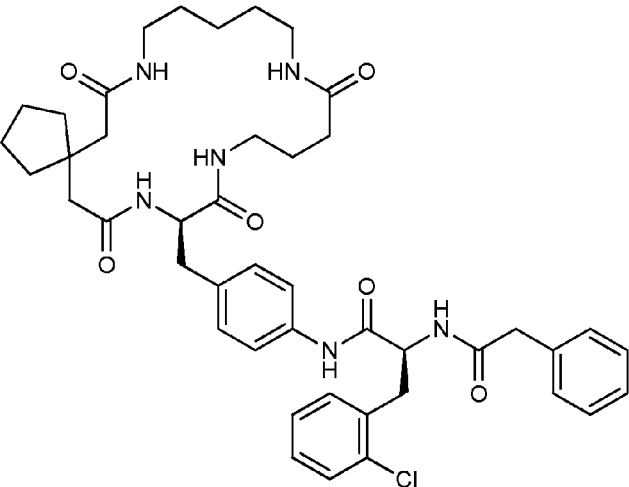
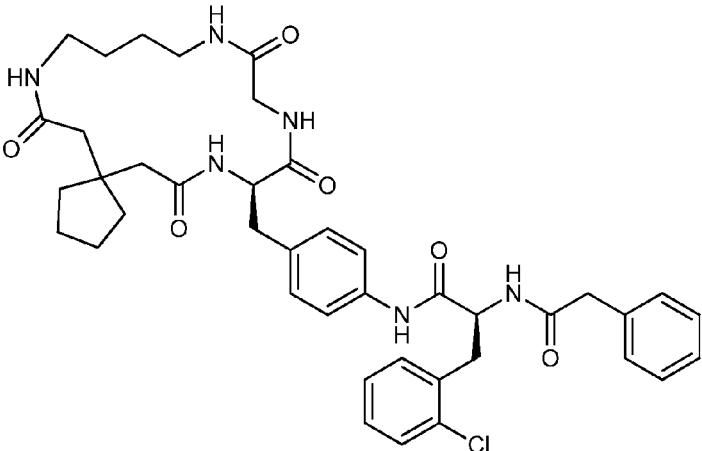
Compound No.	Structure
161	 <p>Chemical structure of Compound 161: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group. This is linked via a chiral center to a benzyl group, which is further connected to a 2-chlorophenyl ring. The structure also includes a 2-phenylacetamido group and a long-chain amide linkage.</p>
162	 <p>Chemical structure of Compound 162: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group. This is linked via a chiral center to a benzyl group, which is further connected to a 2-chlorophenyl ring. The structure also includes a 2-phenylacetamido group and a long-chain amide linkage, differing from Compound 161 in the amide chain configuration.</p>

FIG. 12-26

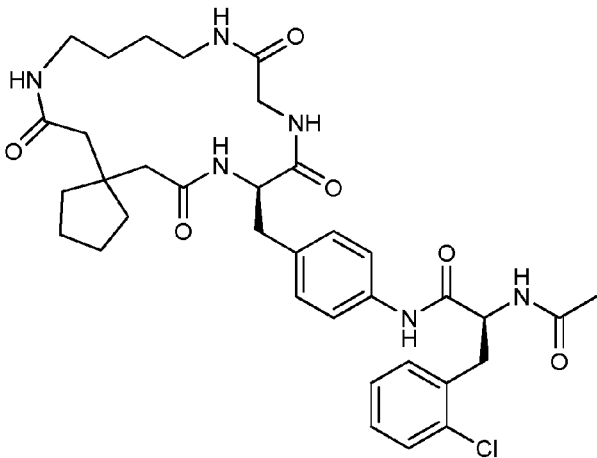
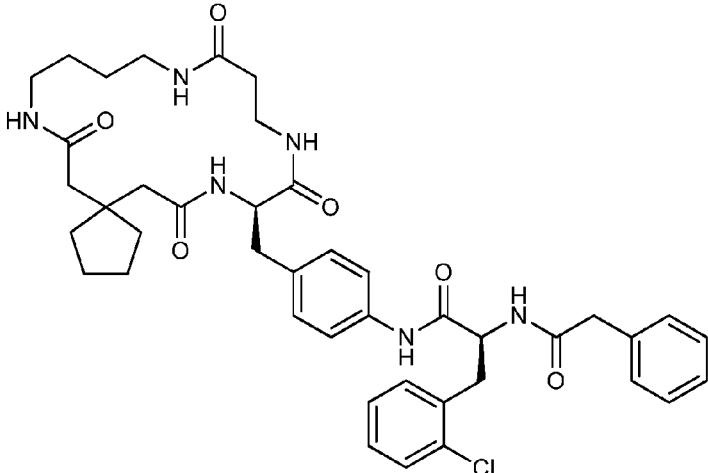
Compound No.	Structure
163	 <p>Chemical structure of Compound 163: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (HN-C(=O)-) and a side chain containing two amide linkages. The side chain includes a 4-phenyl group, a 2-chlorophenyl group, and a terminal amide group (NH-C(=O)-CH₃).</p>
164	 <p>Chemical structure of Compound 164: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (HN-C(=O)-) and a side chain containing two amide linkages. The side chain includes a 4-phenyl group, a 2-chlorophenyl group, and a terminal amide group (NH-C(=O)-CH₂-C₆H₅).</p>

FIG. 12-27

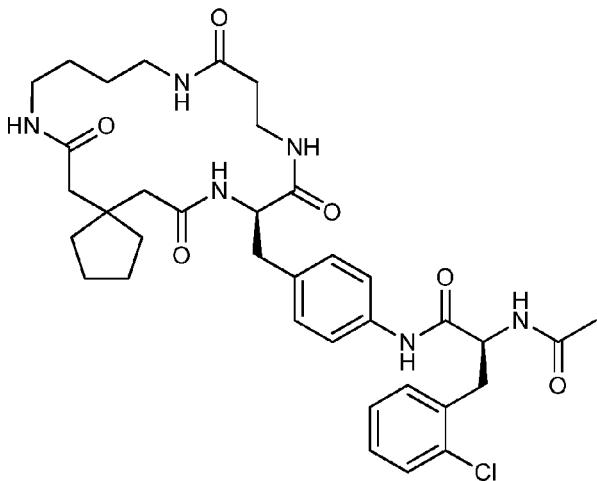
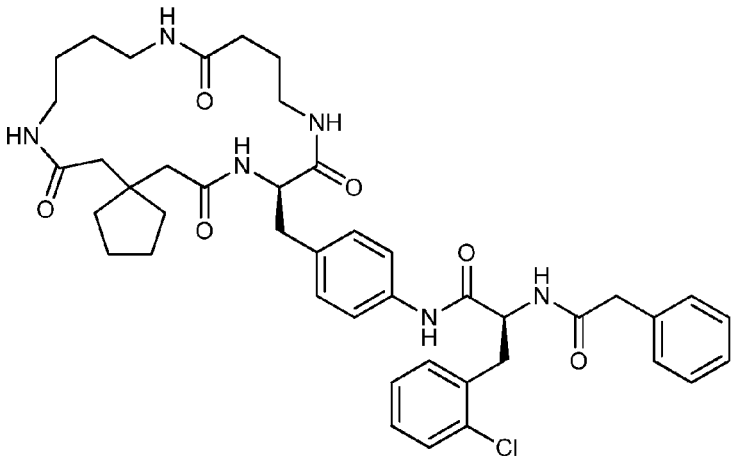
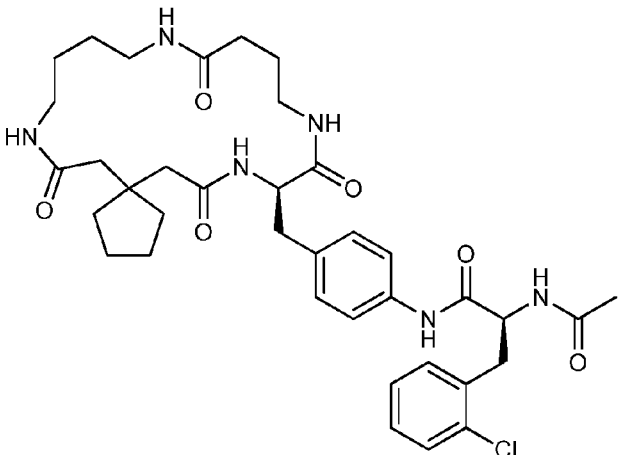
Compound No.	Structure
165	
166	
167	

FIG. 12-28

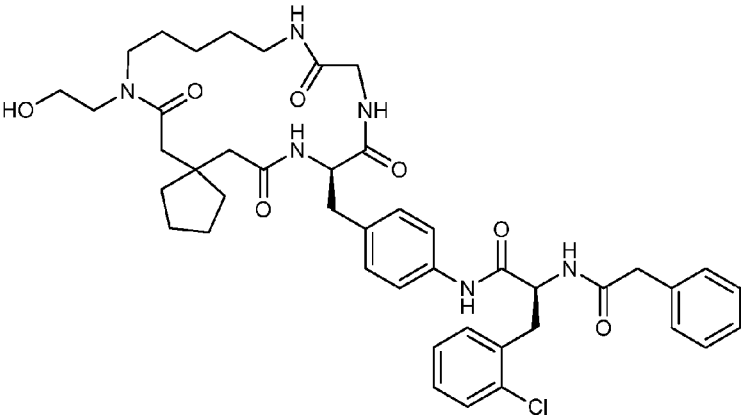
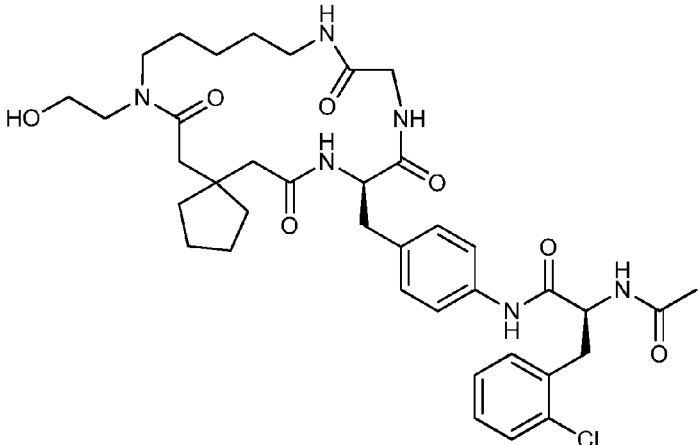
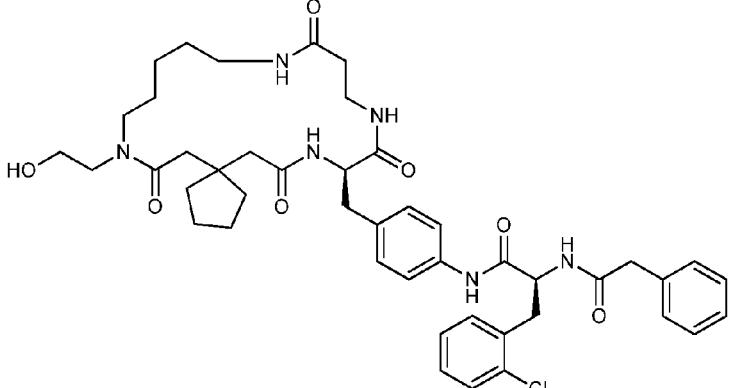
Compound No.	Structure
168	 <p>Chemical structure of compound 168: A complex molecule featuring a central amide linkage. The left side includes a hydroxymethyl group (HO-CH₂-) attached to a nitrogen atom, which is part of a larger amide system. The right side features a benzamide moiety with a chlorine substituent on the benzene ring, connected via an amide bond to a chiral center. The structure also includes a cyclopentyl ring and various amide and ester functional groups.</p>
169	 <p>Chemical structure of compound 169: Similar to compound 168, but with a different amide linkage on the right side, specifically a benzamide moiety with a chlorine substituent on the benzene ring, connected via an amide bond to a chiral center. The structure also includes a cyclopentyl ring and various amide and ester functional groups.</p>
170	 <p>Chemical structure of compound 170: Similar to compound 168, but with a different amide linkage on the right side, specifically a benzamide moiety with a chlorine substituent on the benzene ring, connected via an amide bond to a chiral center. The structure also includes a cyclopentyl ring and various amide and ester functional groups.</p>

FIG. 12-29

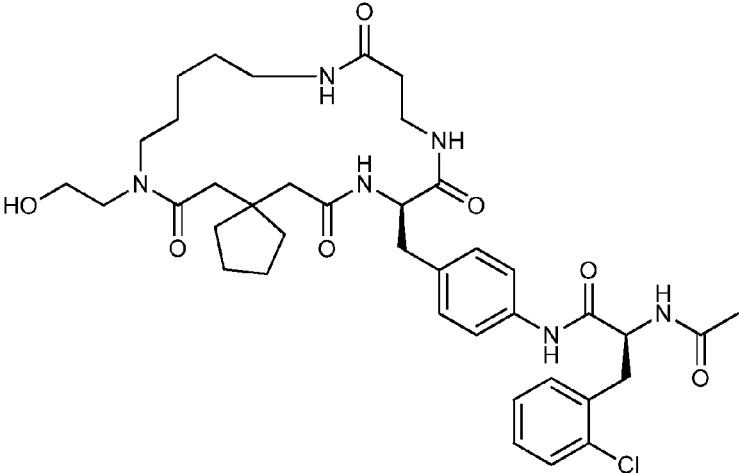
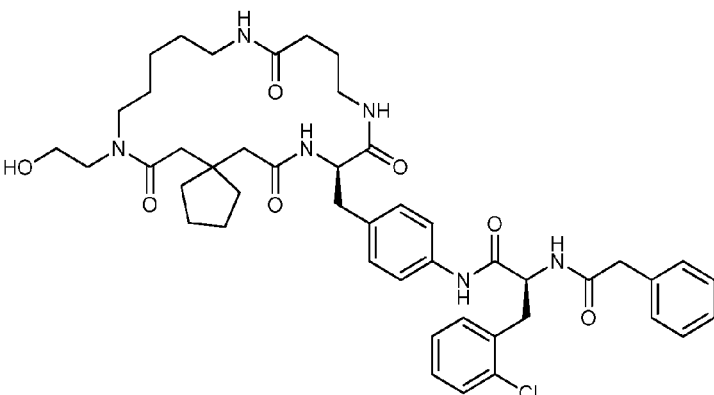
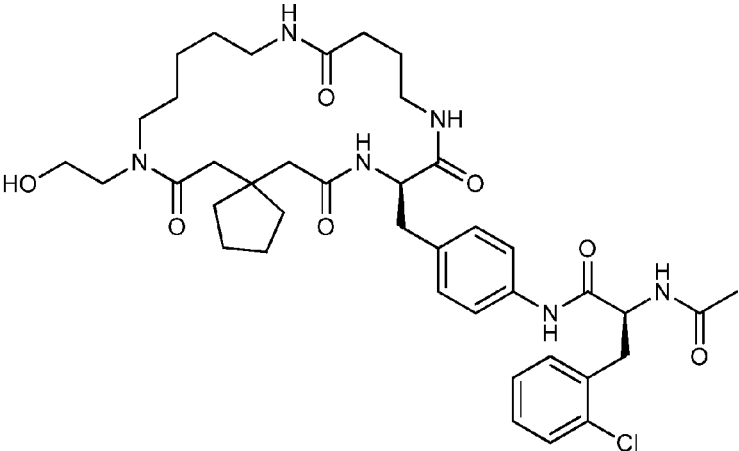
Compound No.	Structure
171	 <p>Chemical structure of Compound 171: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a hydroxyl group (HO-CH2-CH2-) and a carbonyl group (-C(=O)-). Another carbon of the cyclopentane is part of a chain containing a carbonyl group (-C(=O)-) and an amide group (-NH-). The amide group is connected to a side chain that includes a benzamide moiety (a benzene ring attached to a -C(=O)-NH- group) and a 2-chlorophenyl group (a benzene ring with a chlorine atom at the ortho position). The side chain also includes a chiral center with a methyl group (CH3) and a carbonyl group (-C(=O)-).</p>
172	 <p>Chemical structure of Compound 172: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a hydroxyl group (HO-CH2-CH2-) and a carbonyl group (-C(=O)-). Another carbon of the cyclopentane is part of a chain containing a carbonyl group (-C(=O)-) and an amide group (-NH-). The amide group is connected to a side chain that includes a benzamide moiety (a benzene ring attached to a -C(=O)-NH- group) and a 2-chlorophenyl group (a benzene ring with a chlorine atom at the ortho position). The side chain also includes a chiral center with a methyl group (CH3) and a carbonyl group (-C(=O)-).</p>
173	 <p>Chemical structure of Compound 173: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a chain containing a hydroxyl group (HO-CH2-CH2-) and a carbonyl group (-C(=O)-). Another carbon of the cyclopentane is part of a chain containing a carbonyl group (-C(=O)-) and an amide group (-NH-). The amide group is connected to a side chain that includes a benzamide moiety (a benzene ring attached to a -C(=O)-NH- group) and a 2-chlorophenyl group (a benzene ring with a chlorine atom at the ortho position). The side chain also includes a chiral center with a methyl group (CH3) and a carbonyl group (-C(=O)-).</p>

FIG. 12-30

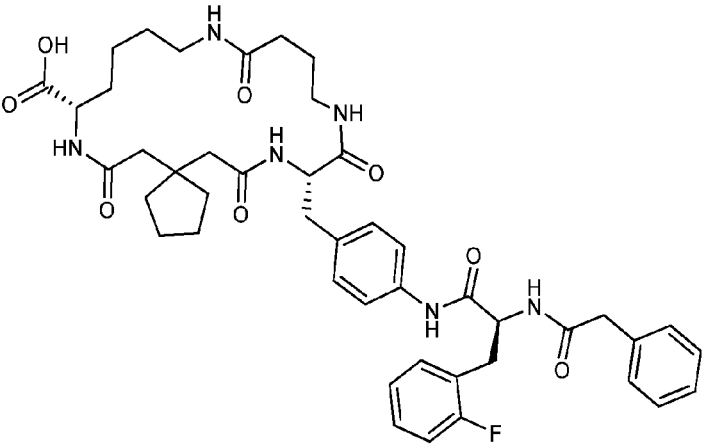
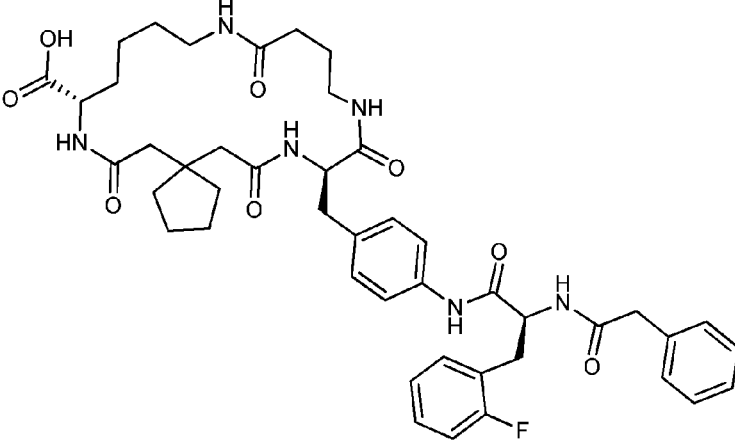
Compound No.	Structure
174	 <p>Chemical structure of Compound 174. It features a cyclopentane ring substituted with two amide groups. One amide is part of a side chain containing a carboxylic acid group and a long alkyl chain. The other amide is part of a side chain containing a benzyl group, which is further substituted with a 2-fluorophenyl group and a benzyl group.</p>
175	 <p>Chemical structure of Compound 175. It is similar to Compound 174, but the stereochemistry at the chiral center adjacent to the benzyl group is different.</p>

FIG. 12-31

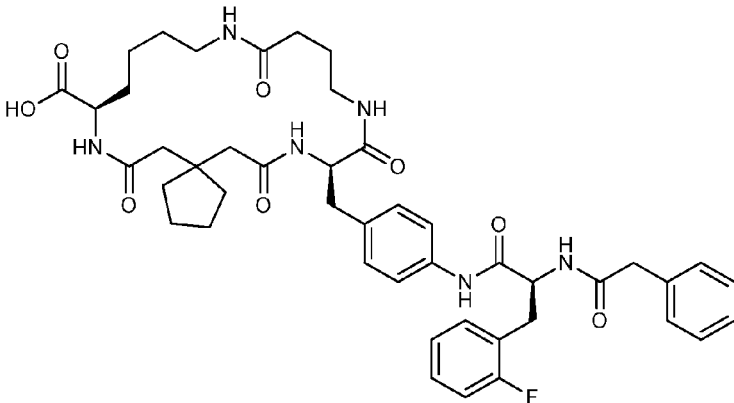
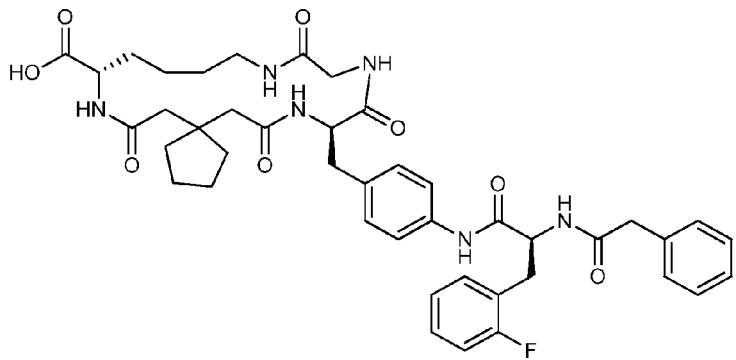
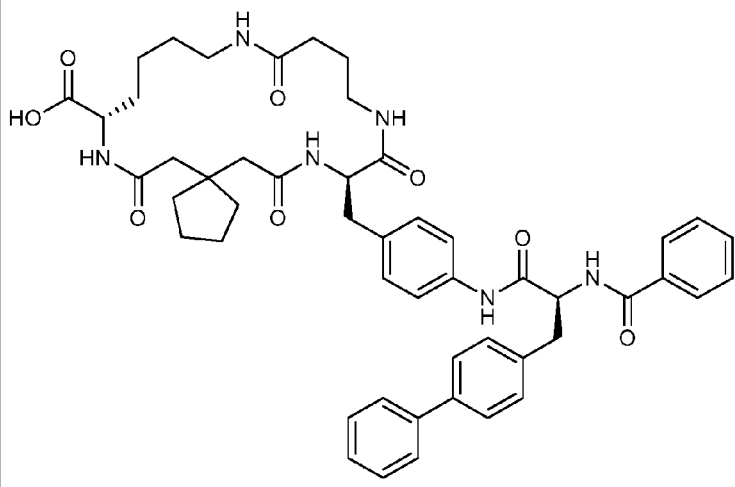
Compound No.	Structure
176	 <p>Chemical structure of Compound 176: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a carboxylic acid group (HO-C(=O)-) and an amide group (-NH-C(=O)-). The other side is connected to an amide group (-NH-C(=O)-) and a carboxylic acid group (HO-C(=O)-). The amide groups are further substituted with a 4-phenyl-2-(2-phenyl-2-oxoethyl)ethyl chain and a 2-phenyl-2-oxoethyl chain.</p>
177	 <p>Chemical structure of Compound 177: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a carboxylic acid group (HO-C(=O)-) and an amide group (-NH-C(=O)-). The other side is connected to an amide group (-NH-C(=O)-) and a carboxylic acid group (HO-C(=O)-). The amide groups are further substituted with a 4-phenyl-2-(2-phenyl-2-oxoethyl)ethyl chain and a 2-phenyl-2-oxoethyl chain.</p>
178	 <p>Chemical structure of Compound 178: A complex molecule featuring a central cyclopentane ring. One side of the ring is connected to a carboxylic acid group (HO-C(=O)-) and an amide group (-NH-C(=O)-). The other side is connected to an amide group (-NH-C(=O)-) and a carboxylic acid group (HO-C(=O)-). The amide groups are further substituted with a 4-phenyl-2-(2-phenyl-2-oxoethyl)ethyl chain and a 2-phenyl-2-oxoethyl chain.</p>

FIG. 12-32

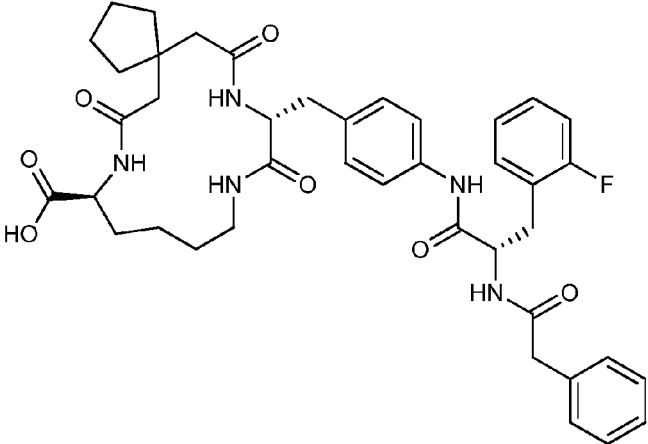
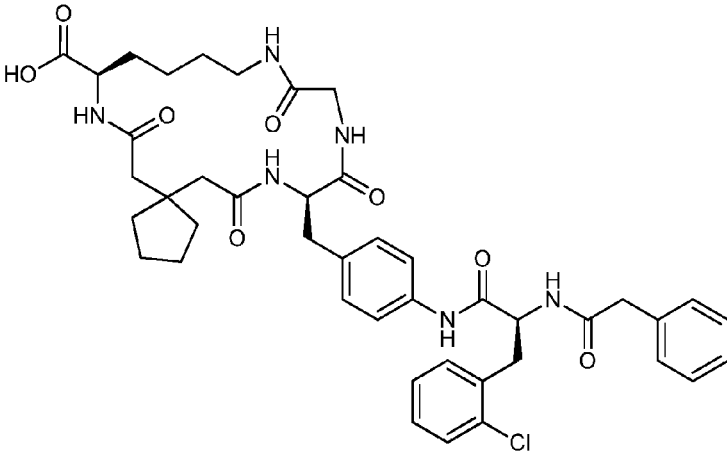
Compound No.	Structure
179	 <p>Chemical structure of Compound 179: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and a carbonyl group. This is linked via an amide bond to a chain containing a fluorophenyl group and a benzyl group.</p>
180	 <p>Chemical structure of Compound 180: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and a carbonyl group. This is linked via an amide bond to a chain containing a chlorophenyl group and a benzyl group.</p>

FIG. 12-33

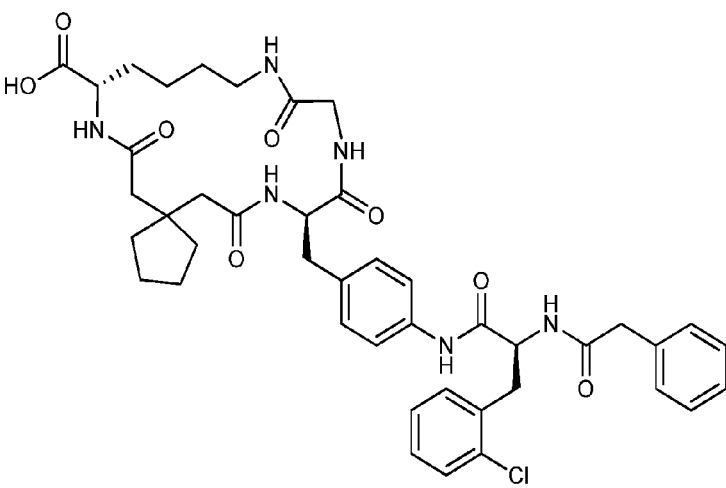
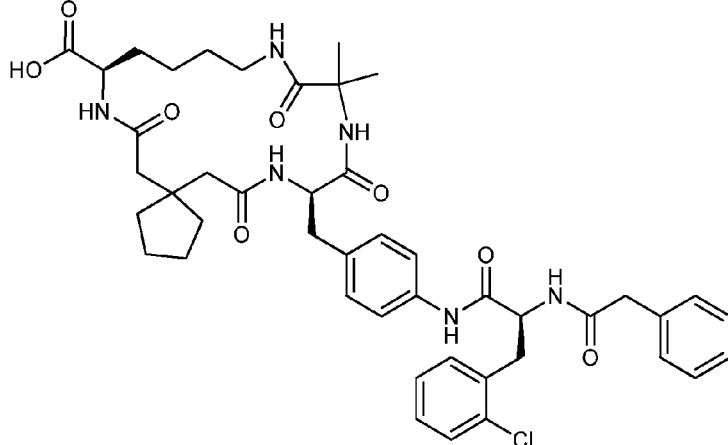
Compound No.	Structure
181	 <p>Chemical structure of Compound 181. It features a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and a side chain containing two amide bonds. The side chain includes a 4-phenyl group, a 2-chlorophenyl group, and a benzyl group. Stereochemistry is indicated with wedges and dashes.</p>
182	 <p>Chemical structure of Compound 182. It features a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and a side chain containing two amide bonds. The side chain includes a 4-phenyl group, a 2-chlorophenyl group, and a benzyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-34

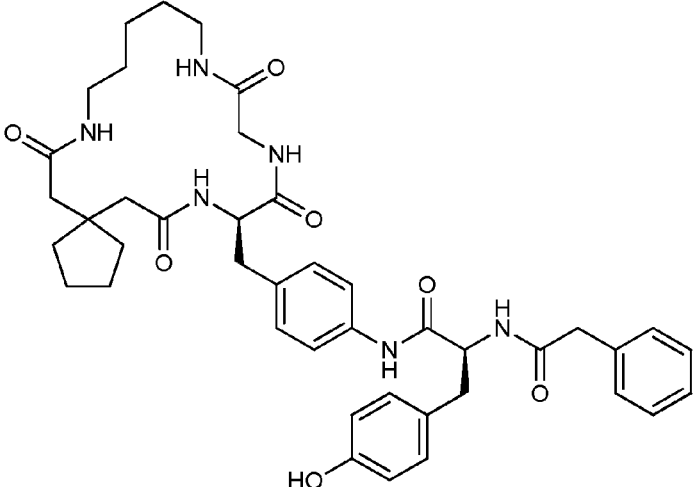
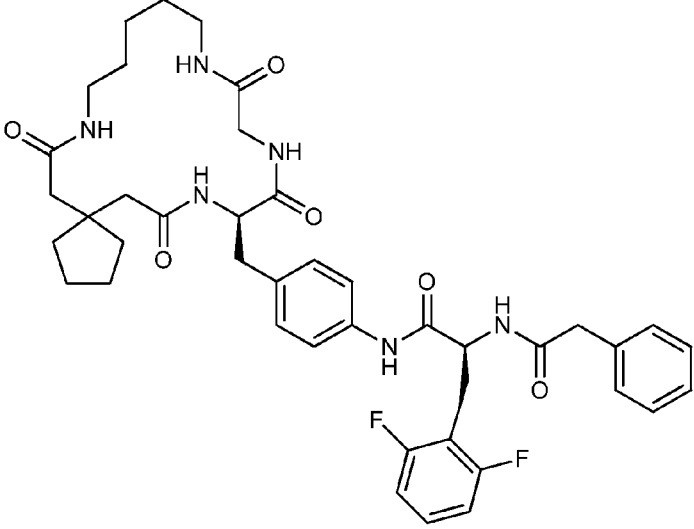
Compound No.	Structure
183	 <p>Chemical structure of Compound 183. It features a cyclopentane ring substituted with a 1,4-bis(carbamoyl)butyl group and a 1,4-bis(carbamoyl)-2-((4-((4-hydroxyphenyl)amino)-2-oxo-1-phenylethyl)amino)-2-oxo-1-phenylethyl group.</p>
184	 <p>Chemical structure of Compound 184. It is similar to Compound 183, but the phenyl ring in the side chain is substituted with two fluorine atoms at the 2 and 6 positions.</p>

FIG. 12-35

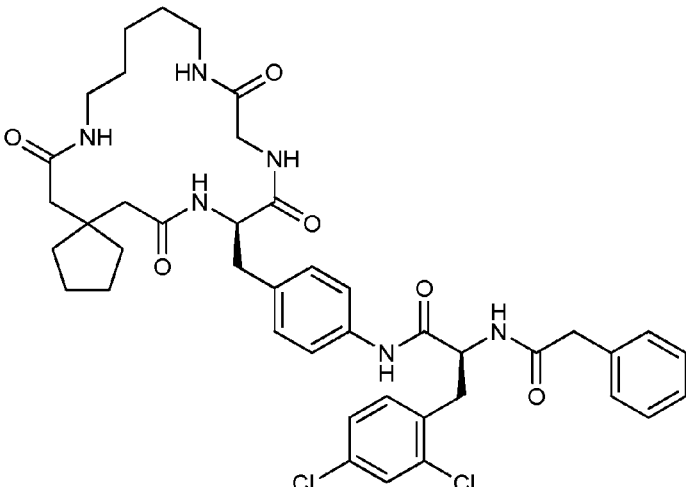
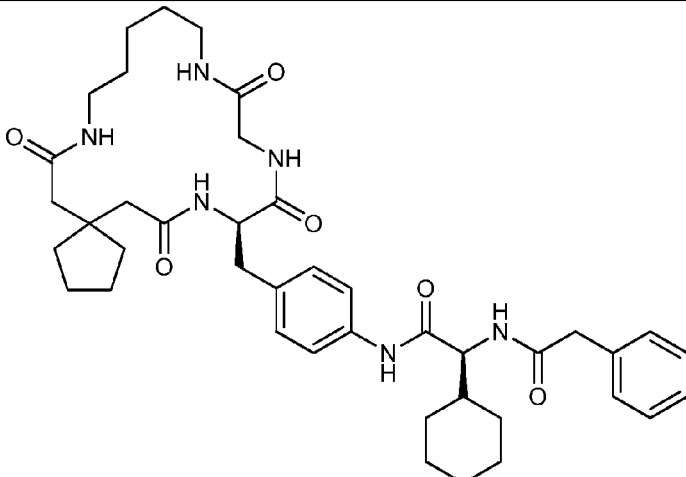
Compound No.	Structure
185	 <p>Chemical structure of Compound 185: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(carbamoyl)propyl group and a 1-carbamoyl-2-(2-((2-chloro-4-chlorophenyl)amino)-2-oxoethyl)ethyl group. The 2-chloro-4-chlorophenyl group is further substituted with a 1-carbamoyl-2-(2-((2-phenylacetamido)-2-oxoethyl)ethyl)ethyl group.</p>
186	 <p>Chemical structure of Compound 186: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(carbamoyl)propyl group and a 1-carbamoyl-2-(2-((2-cyclohexylamino)-2-oxoethyl)ethyl)ethyl group. The 2-cyclohexylamino group is further substituted with a 1-carbamoyl-2-(2-((2-phenylacetamido)-2-oxoethyl)ethyl)ethyl group.</p>

FIG. 12-36

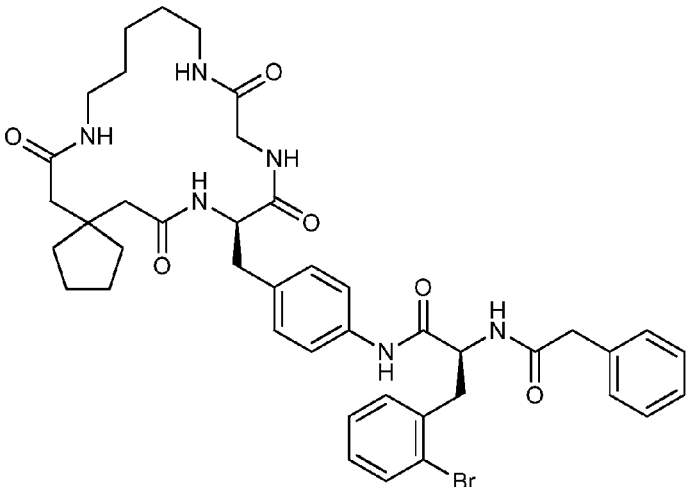
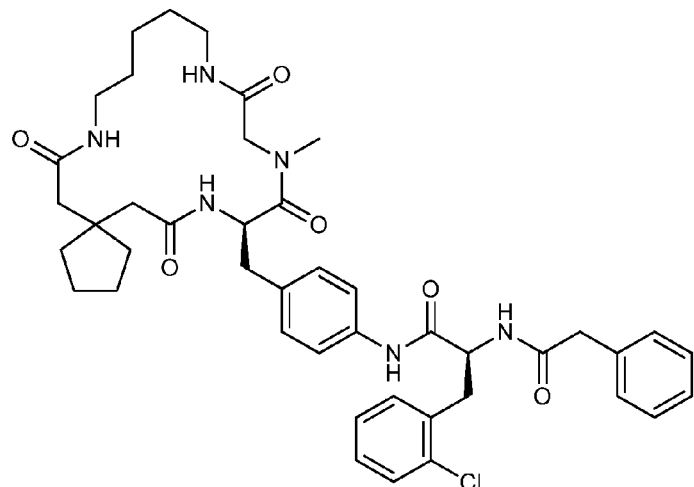
Compound No.	Structure
187	 <p>Chemical structure of Compound 187. It features a complex molecule with a central amide linkage. On the left, there is a cyclopentyl ring connected to a chain containing two amide groups. The central part of the molecule includes a benzamide moiety linked to a 2-bromophenyl group. On the right, there is a benzamide moiety linked to a benzyl group. Stereochemistry is indicated with wedges and dashes.</p>
188	 <p>Chemical structure of Compound 188. It is similar to Compound 187 but features a 2-chlorophenyl group instead of a 2-bromophenyl group. The rest of the molecule, including the cyclopentyl ring, amide linkages, and benzamide moieties, is identical to Compound 187. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-37

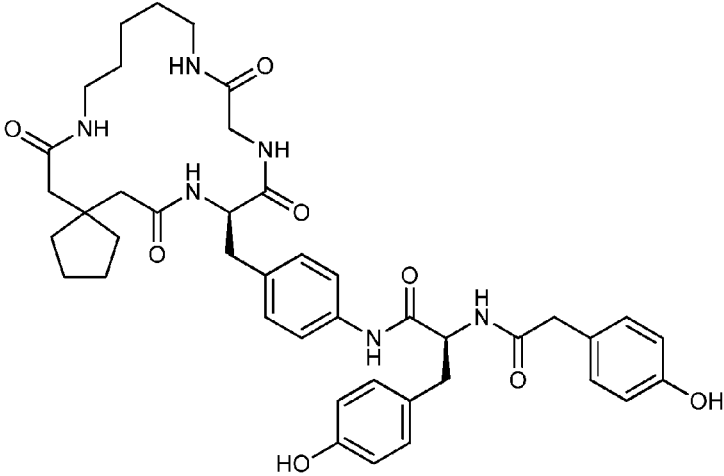
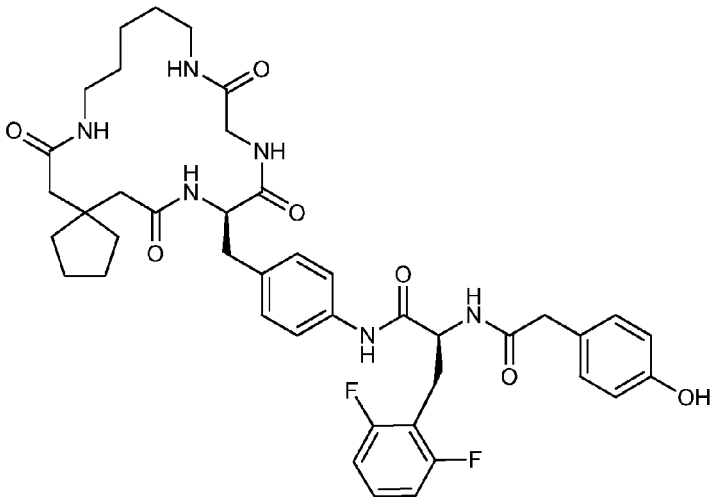
Compound No.	Structure
189	 <p>Chemical structure of Compound 189: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(amide)propan-2-yl group and a 1,3-bis(amide)propan-2-yl group. The 1,3-bis(amide)propan-2-yl group is further substituted with a 4-(4-hydroxyphenyl)phenyl group and a 4-(4-hydroxyphenyl)phenyl group.</p>
190	 <p>Chemical structure of Compound 190: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(amide)propan-2-yl group and a 1,3-bis(amide)propan-2-yl group. The 1,3-bis(amide)propan-2-yl group is further substituted with a 4-(2,6-difluorophenyl)phenyl group and a 4-(4-hydroxyphenyl)phenyl group.</p>

FIG. 12-38

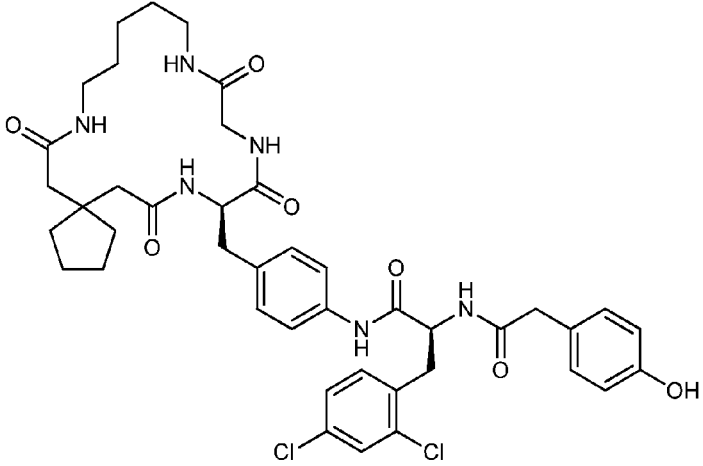
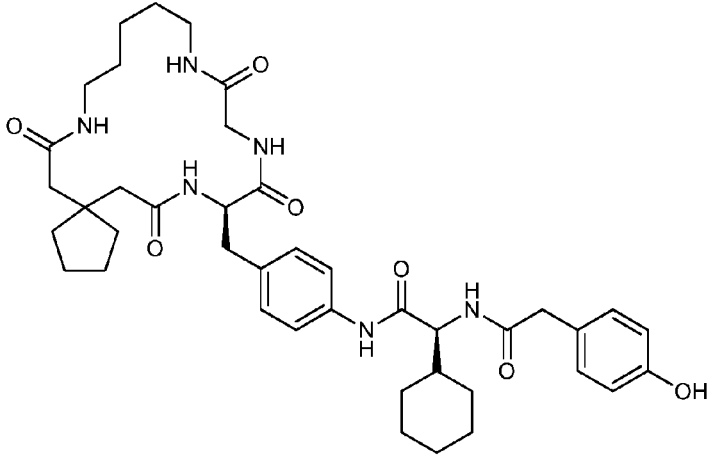
Compound No.	Structure
191	 <p>Chemical structure of Compound 191: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide chain. The right side features a benzene ring substituted with a chlorine atom and a hydroxyl group, connected via an amide linkage to a cyclohexyl ring.</p>
192	 <p>Chemical structure of Compound 192: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide chain. The right side features a benzene ring substituted with a chlorine atom and a hydroxyl group, connected via an amide linkage to a cyclohexyl ring.</p>

FIG. 12-39

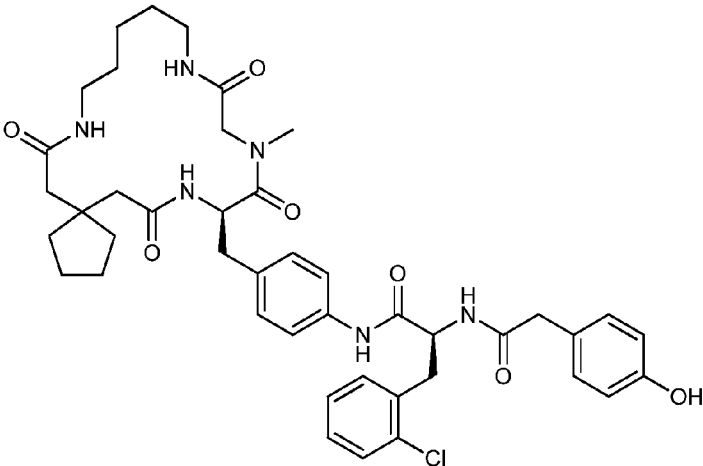
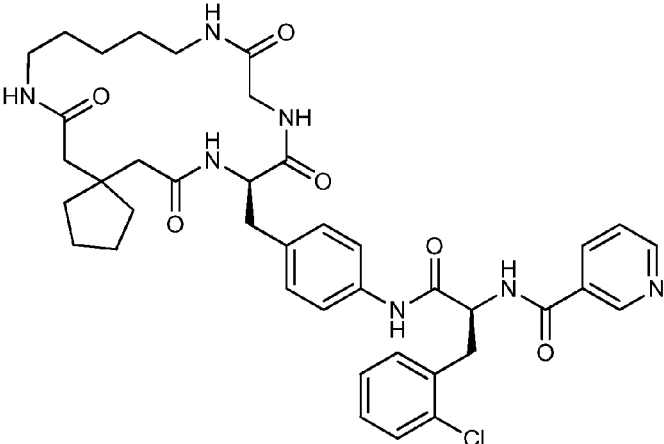
Compound No.	Structure
193	 <p>Chemical structure of Compound 193: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-CO-CH2-). This is linked via an amide bond to a chiral center (CH) which is also substituted with a methyl group and a benzyl group. The benzyl group is further substituted with a 2-chlorophenyl ring. The 2-chlorophenyl ring is linked via an amide bond to a chiral center (CH) which is also substituted with a hydrogen atom and a 4-hydroxybenzyl group. The 4-hydroxybenzyl group is linked via an amide bond to a 4-hydroxyphenyl ring.</p>
194	 <p>Chemical structure of Compound 194: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-CO-CH2-). This is linked via an amide bond to a chiral center (CH) which is also substituted with a hydrogen atom and a benzyl group. The benzyl group is further substituted with a 2-chlorophenyl ring. The 2-chlorophenyl ring is linked via an amide bond to a chiral center (CH) which is also substituted with a hydrogen atom and a 4-pyridylmethyl group. The 4-pyridylmethyl group is linked via an amide bond to a 4-pyridyl ring.</p>

FIG. 12-40

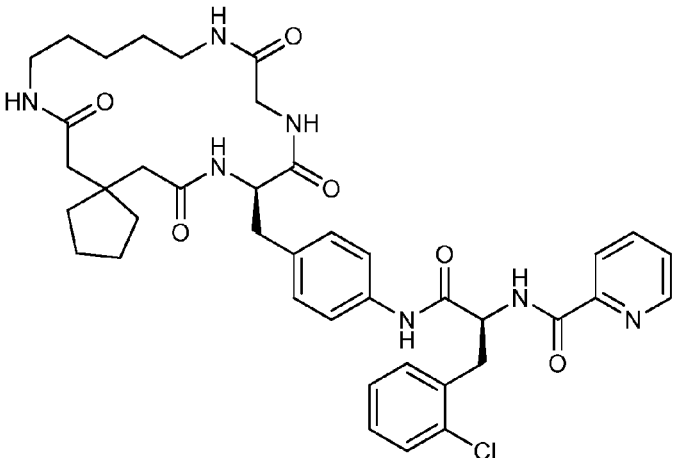
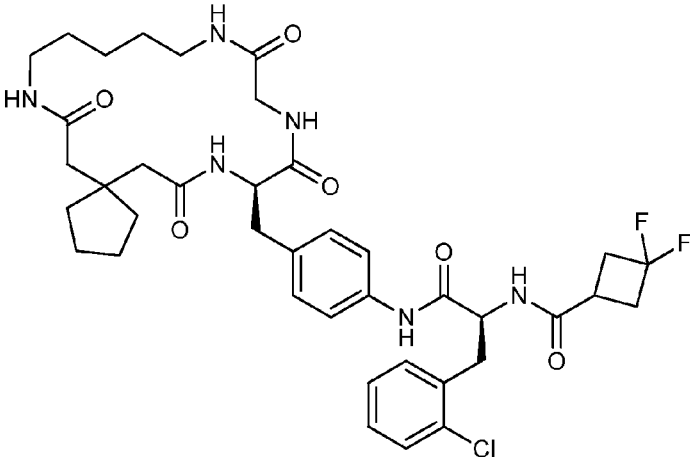
Compound No.	Structure
195	 <p>Chemical structure of Compound 195: A complex molecule featuring a 1,4-bis(amide)heptane chain. One amide is attached to a cyclopentylmethyl group, and the other is attached to a 2-chlorophenylmethyl group. The 2-chlorophenylmethyl group is further linked to a 4-((2-chlorophenylmethyl)carbamoyl)phenyl group, which is connected to a 2-chlorophenylmethyl group, which is finally linked to a 4-pyridylmethyl group.</p>
196	 <p>Chemical structure of Compound 196: A complex molecule featuring a 1,4-bis(amide)heptane chain. One amide is attached to a cyclopentylmethyl group, and the other is attached to a 2-chlorophenylmethyl group. The 2-chlorophenylmethyl group is further linked to a 4-((2-chlorophenylmethyl)carbamoyl)phenyl group, which is connected to a 2-chlorophenylmethyl group, which is finally linked to a 4-(difluoromethyl)phenyl group.</p>

FIG. 12-41

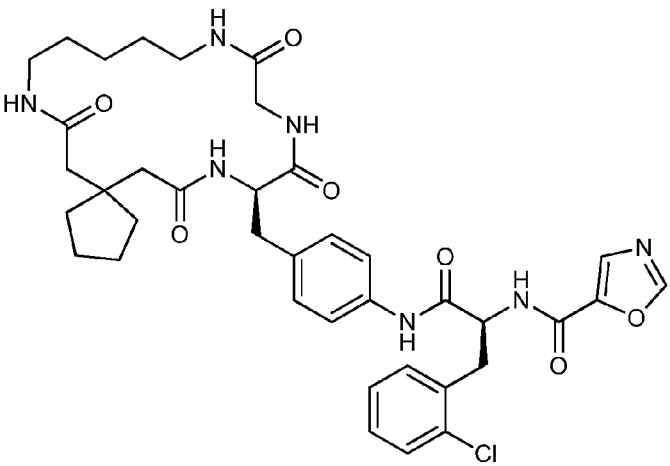
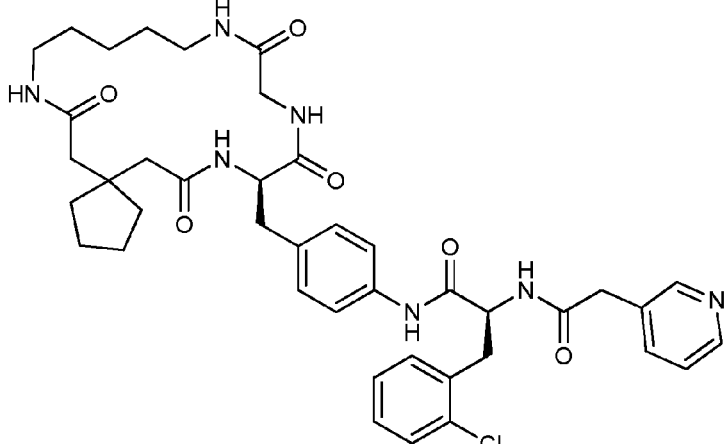
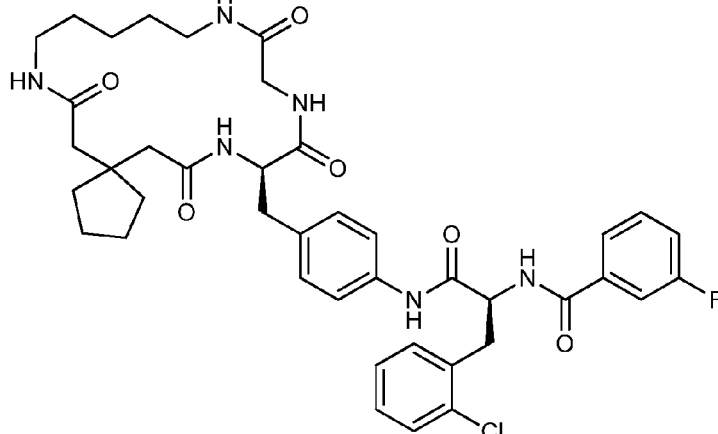
Compound No.	Structure
197	 <p>Chemical structure of Compound 197: A complex molecule featuring a central bicyclic amide core (a cyclopentane ring fused to a cyclohexane ring, with an amide group attached to the cyclohexane ring). This core is linked via a long chain to a benzamide moiety, which is further connected to a 2-chlorophenyl group. The structure also includes a 2-furyl group and a 2-pyridyl group.</p>
198	 <p>Chemical structure of Compound 198: A complex molecule featuring a central bicyclic amide core (a cyclopentane ring fused to a cyclohexane ring, with an amide group attached to the cyclohexane ring). This core is linked via a long chain to a benzamide moiety, which is further connected to a 2-chlorophenyl group. The structure also includes a 2-pyridyl group and a 2-furyl group.</p>
199	 <p>Chemical structure of Compound 199: A complex molecule featuring a central bicyclic amide core (a cyclopentane ring fused to a cyclohexane ring, with an amide group attached to the cyclohexane ring). This core is linked via a long chain to a benzamide moiety, which is further connected to a 2-chlorophenyl group. The structure also includes a 2-furyl group and a 2-pyridyl group.</p>

FIG. 12-42

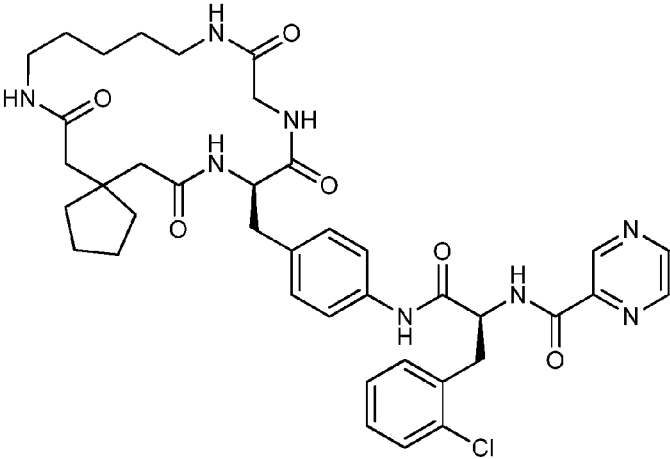
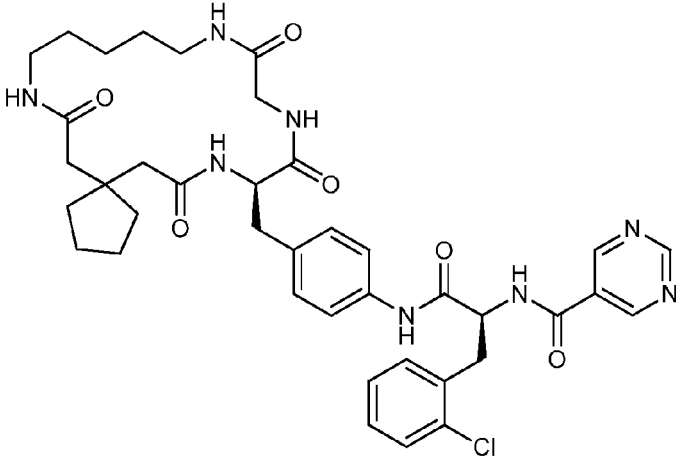
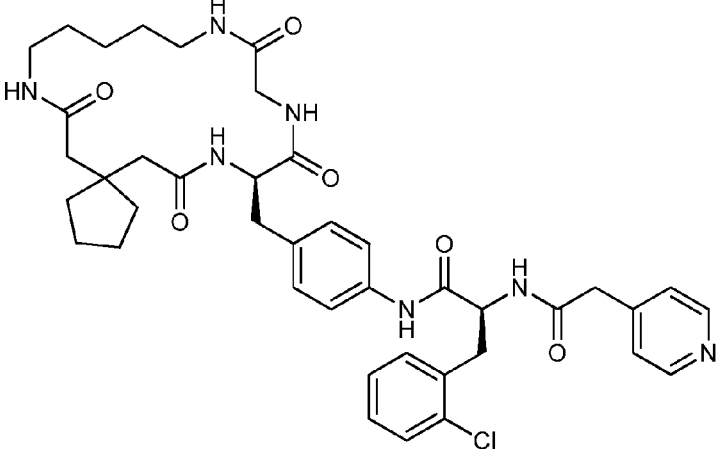
Compound No.	Structure
200	 <p>Chemical structure of Compound 200: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a terminal amine. The right side features a benzimidazole core substituted with a 4-chlorophenyl group and a pyrimidin-2-ylmethyl group.</p>
201	 <p>Chemical structure of Compound 201: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a terminal amine. The right side features a benzimidazole core substituted with a 4-chlorophenyl group and a pyrimidin-2-ylmethyl group.</p>
202	 <p>Chemical structure of Compound 202: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a terminal amine. The right side features a benzimidazole core substituted with a 4-chlorophenyl group and a 3-pyridylmethyl group.</p>

FIG. 12-43

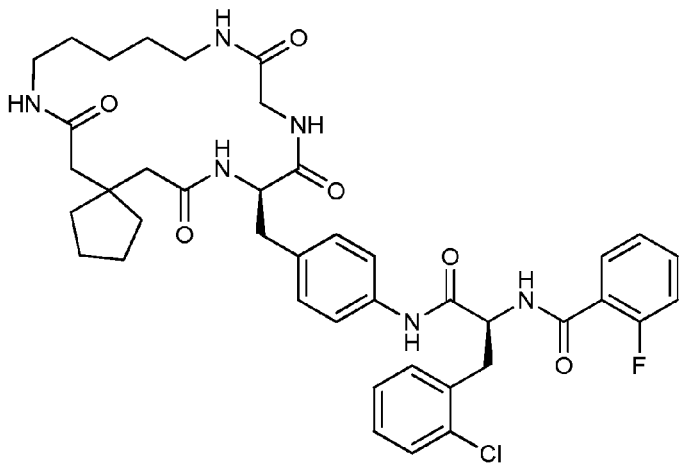
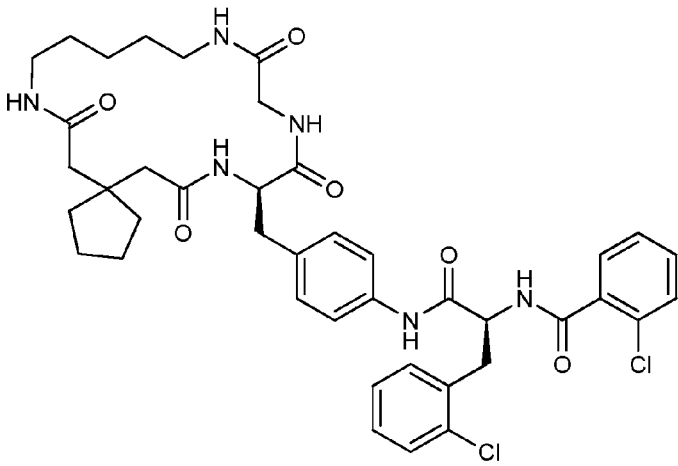
Compound No.	Structure
203	 <p>Chemical structure of Compound 203: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety linked to a 2-chlorophenyl group, which is further connected to a 2-fluorophenyl group via an amide bond.</p>
204	 <p>Chemical structure of Compound 204: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety linked to a 2-chlorophenyl group, which is further connected to a 2-chlorophenyl group via an amide bond.</p>

FIG. 12-44

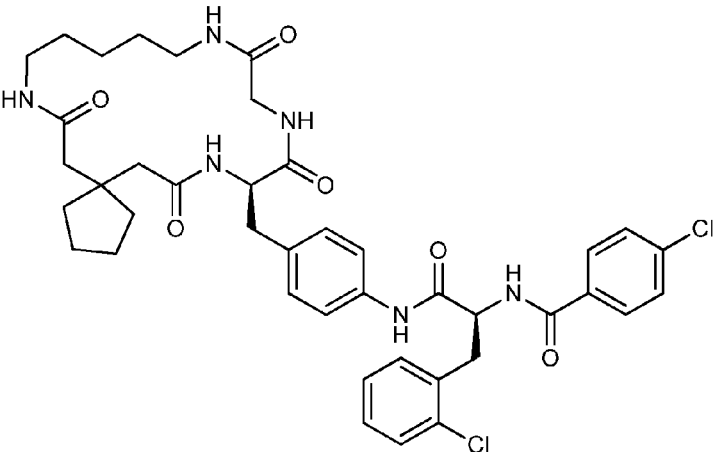
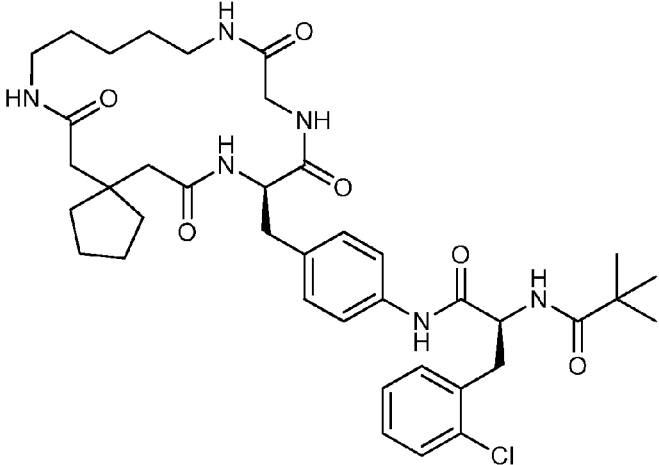
Compound No.	Structure
205	 <p>Chemical structure of Compound 205: A complex molecule featuring a cyclopentane ring substituted with a 6-oxoheptan-1-ylideneamino group and a 2-((2-chlorophenyl)amino)-3-((4-chlorophenyl)amino)propanamido group. The molecule also includes a 2-chlorophenyl group and a 4-chlorophenyl group.</p>
206	 <p>Chemical structure of Compound 206: A complex molecule featuring a cyclopentane ring substituted with a 6-oxoheptan-1-ylideneamino group and a 2-((2-chlorophenyl)amino)-3-((tert-butylamino)propanamido group. The molecule also includes a 2-chlorophenyl group and a tert-butyl group.</p>

FIG. 12-45

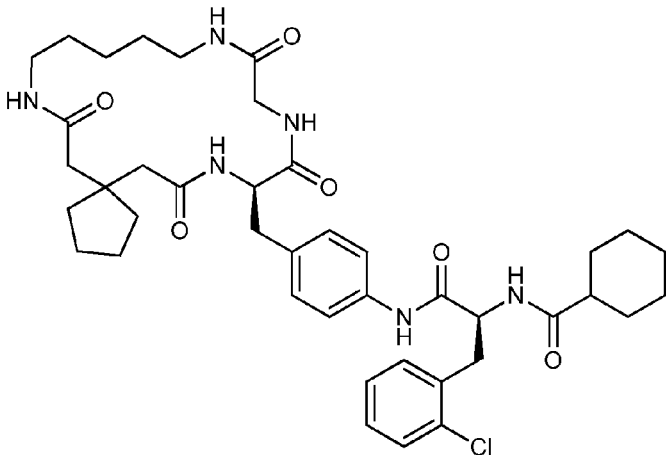
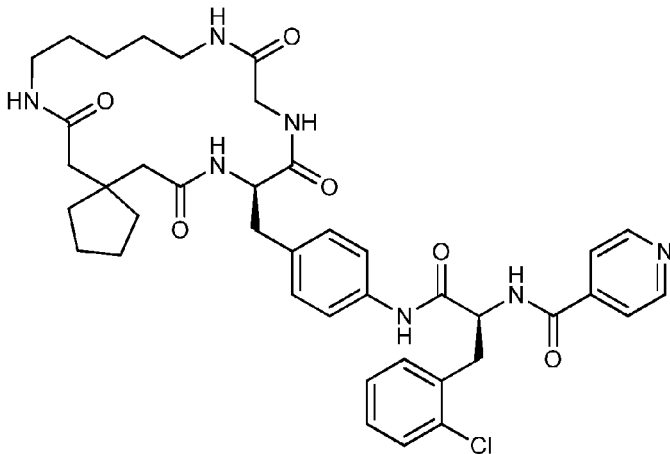
Compound No.	Structure
207	 <p>Chemical structure of Compound 207: A complex molecule featuring a central amide linkage. The left side consists of a 6-aminohexanoic acid derivative (HN-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-C(=O)-NH-) attached to a cyclopentyl ring. The right side features a 2-chlorophenyl group connected to a pyridine-2-carboxamide moiety, which is further linked to a cyclohexyl group via an amide bond.</p>
208	 <p>Chemical structure of Compound 208: A complex molecule featuring a central amide linkage. The left side consists of a 6-aminohexanoic acid derivative (HN-CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-C(=O)-NH-) attached to a cyclopentyl ring. The right side features a 2-chlorophenyl group connected to a pyridine-2-carboxamide moiety, which is further linked to a pyridine-2-carboxamide moiety via an amide bond.</p>

FIG. 12-46

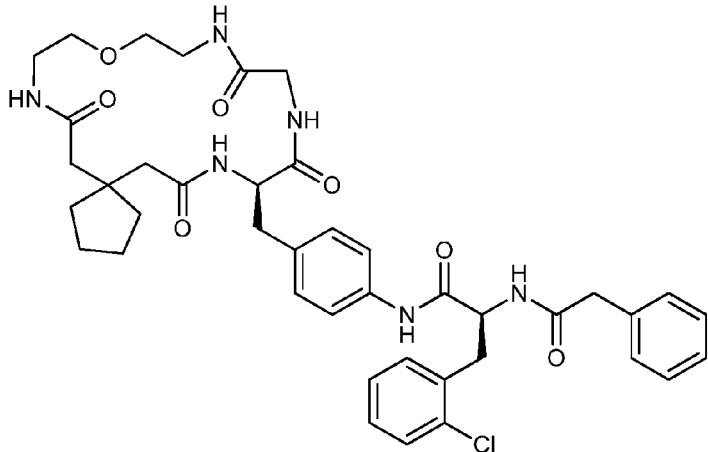
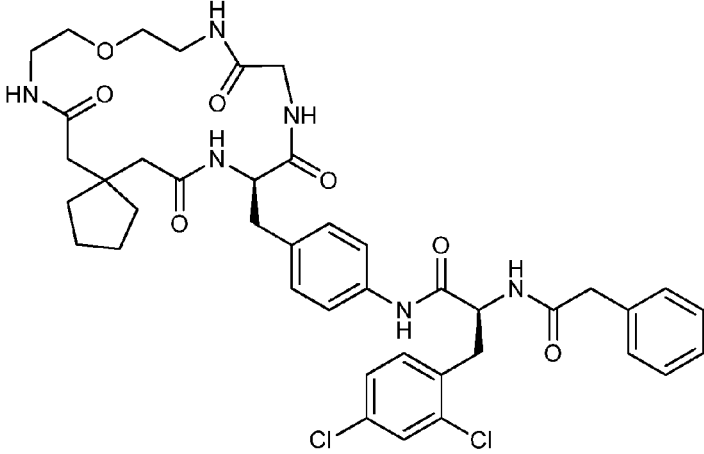
Compound No.	Structure
209	 <p>Chemical structure of Compound 209: A complex molecule featuring a cyclopentane ring substituted with a carbamate group (HN-C(=O)-CH2-) and a carbonyl group (-C(=O)-CH2-). This carbonyl group is part of a larger chain that includes a benzyl group (CH2-C6H5) and a 4-chlorophenyl group (C6H4-Cl). The molecule also contains a 3-phenylpropanamide moiety (CH2-CH2-C(=O)-NH-CH2-C6H5) and a carbamate group (HN-C(=O)-CH2-).</p>
210	 <p>Chemical structure of Compound 210: A complex molecule featuring a cyclopentane ring substituted with a carbamate group (HN-C(=O)-CH2-) and a carbonyl group (-C(=O)-CH2-). This carbonyl group is part of a larger chain that includes a benzyl group (CH2-C6H5) and a 3,5-dichlorophenyl group (C6H3Cl2). The molecule also contains a 3-phenylpropanamide moiety (CH2-CH2-C(=O)-NH-CH2-C6H5) and a carbamate group (HN-C(=O)-CH2-).</p>

FIG. 12-47

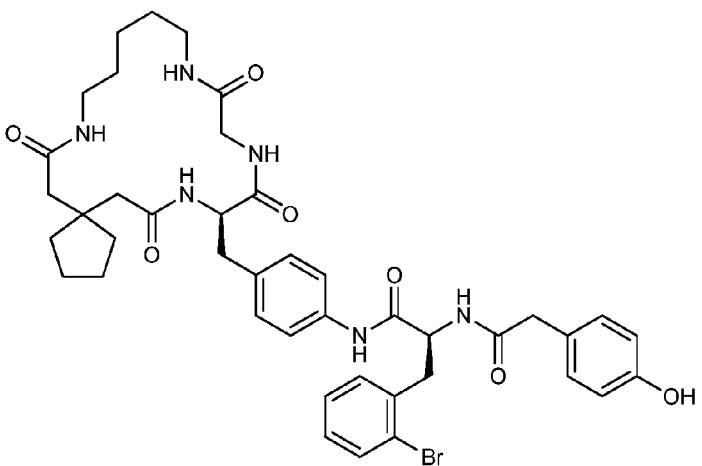
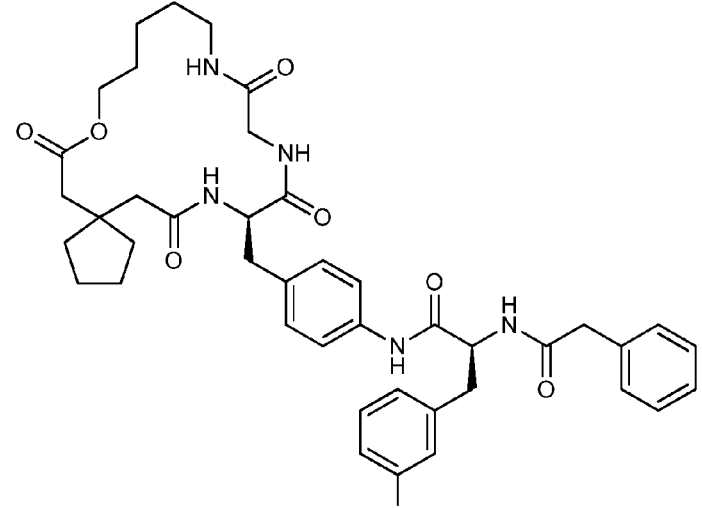
Compound No.	Structure
211	 <p>Chemical structure of Compound 211: A complex molecule featuring a cyclopentyl ring connected to a chain containing multiple amide and carbamate groups. The chain includes a 4-bromophenyl group, a 2-bromophenyl group, and a 4-hydroxyphenyl group.</p>
212	 <p>Chemical structure of Compound 212: A complex molecule featuring a cyclopentyl ring connected to a chain containing multiple amide and carbamate groups. The chain includes a 4-chlorophenyl group and a phenyl group.</p>

FIG. 12-48

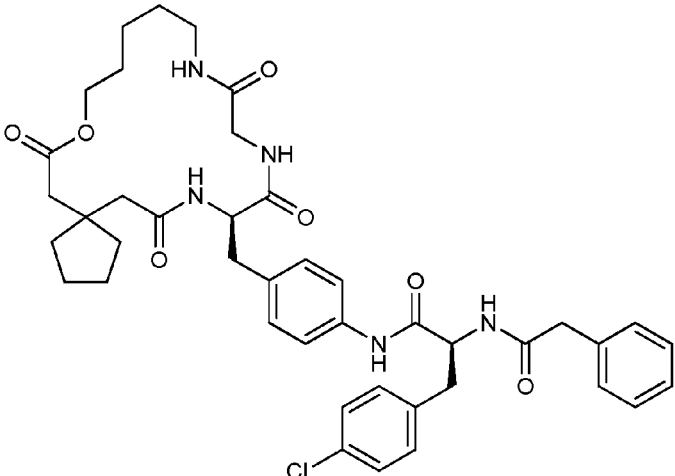
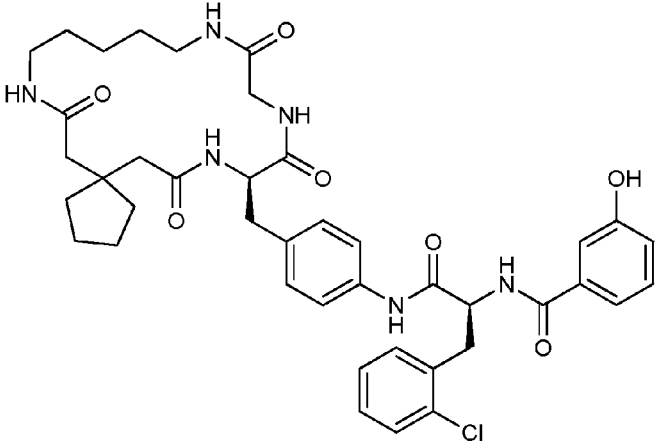
Compound No.	Structure
213	 <p>Chemical structure of Compound 213: A complex molecule featuring a cyclopentyl ring connected to a chain containing multiple amide and ester linkages. The chain includes a 4-chlorophenyl group and a 4-phenylbutanamide moiety.</p>
214	 <p>Chemical structure of Compound 214: A complex molecule featuring a cyclopentyl ring connected to a chain containing multiple amide and ester linkages. The chain includes a 4-chlorophenyl group and a 4-hydroxyphenyl moiety.</p>

FIG. 12-49

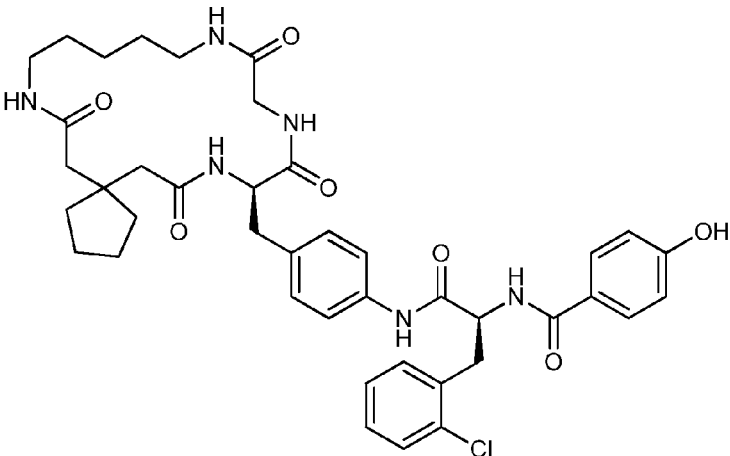
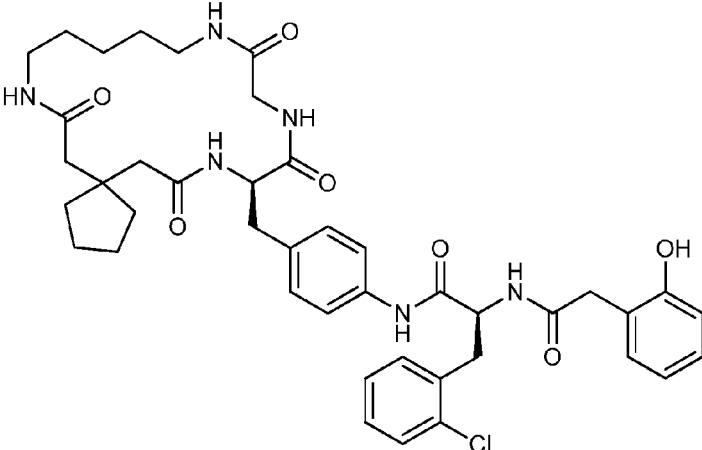
Compound No.	Structure
215	 <p>Chemical structure of Compound 215: A complex molecule featuring a central benzamide core. The benzamide is substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group. The benzamide is further substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group. The benzamide is further substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group.</p>
216	 <p>Chemical structure of Compound 216: A complex molecule featuring a central benzamide core. The benzamide is substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group. The benzamide is further substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group. The benzamide is further substituted with a 4-hydroxyphenyl group and a 2-chlorophenyl group.</p>

FIG. 12-50

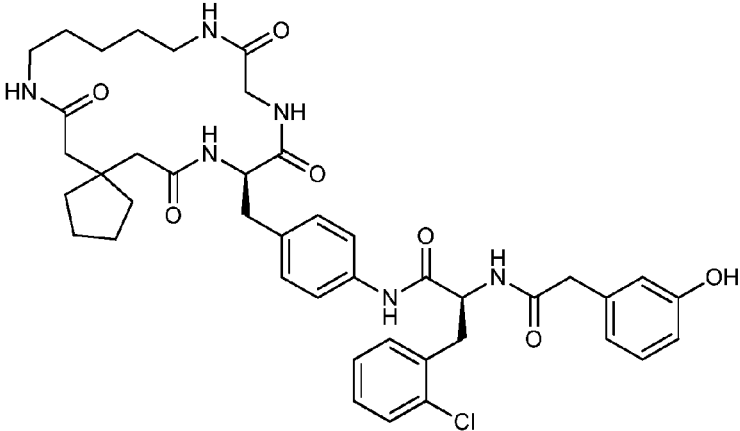
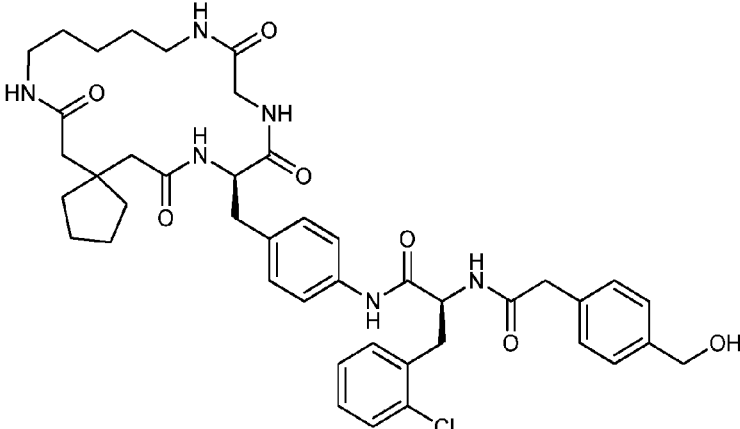
Compound No.	Structure
217	 <p>Chemical structure of Compound 217: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (HN-C(=O)-) and a carboxylic acid group (-COOH). The carboxamide group is further substituted with a long chain containing a secondary amide (NH-C(=O)-) and a carboxylic acid group (-COOH). The carboxylic acid group is further substituted with a benzene ring, which is in turn substituted with a carboxamide group (NH-C(=O)-). The carboxamide group is further substituted with a benzene ring, which is in turn substituted with a carboxylic acid group (-COOH). The carboxylic acid group is further substituted with a benzene ring, which is in turn substituted with a carboxylic acid group (-COOH).</p>
218	 <p>Chemical structure of Compound 218: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (HN-C(=O)-) and a carboxylic acid group (-COOH). The carboxamide group is further substituted with a long chain containing a secondary amide (NH-C(=O)-) and a carboxylic acid group (-COOH). The carboxylic acid group is further substituted with a benzene ring, which is in turn substituted with a carboxamide group (NH-C(=O)-). The carboxamide group is further substituted with a benzene ring, which is in turn substituted with a carboxylic acid group (-COOH). The carboxylic acid group is further substituted with a benzene ring, which is in turn substituted with a carboxylic acid group (-COOH).</p>

FIG. 12-51

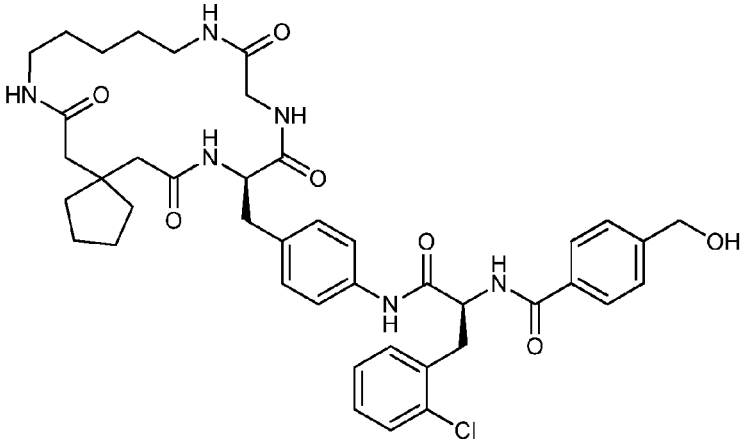
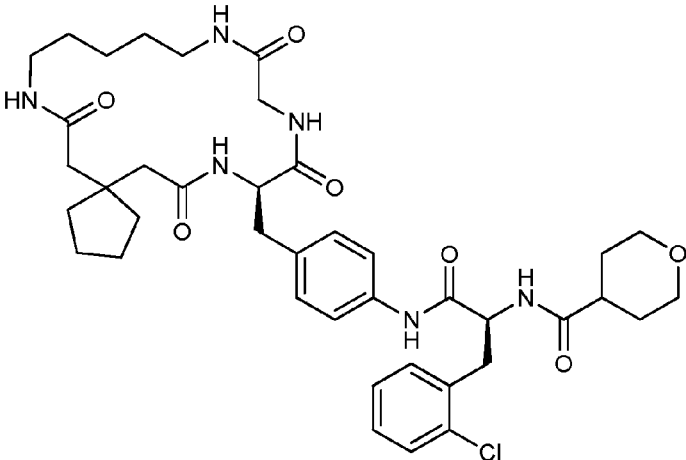
Compound No.	Structure
219	 <p>Chemical structure of Compound 219: A complex molecule featuring a central 1,2-diphenyl-3-chloroethane-1,2-dicarboxamide core. The left phenyl ring is substituted with a 1,1'-bicyclopentyl-2-ylmethyl group via an amide linkage. The right phenyl ring is substituted with a 4-(hydroxymethyl)benzoyl group via an amide linkage. The central ethane chain has a chlorine atom at the 3-position and amide groups at the 1 and 2 positions.</p>
220	 <p>Chemical structure of Compound 220: A complex molecule featuring a central 1,2-diphenyl-3-chloroethane-1,2-dicarboxamide core. The left phenyl ring is substituted with a 1,1'-bicyclopentyl-2-ylmethyl group via an amide linkage. The right phenyl ring is substituted with a 4-(tetrahydro-2H-pyran-2-yl)methyl group via an amide linkage. The central ethane chain has a chlorine atom at the 3-position and amide groups at the 1 and 2 positions.</p>

FIG. 12-52

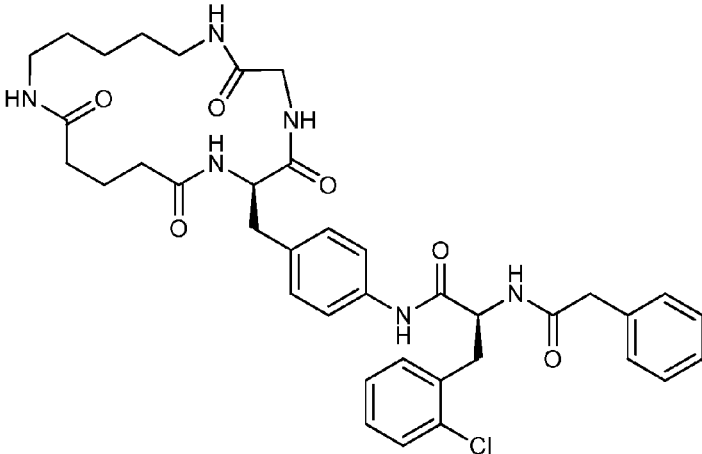
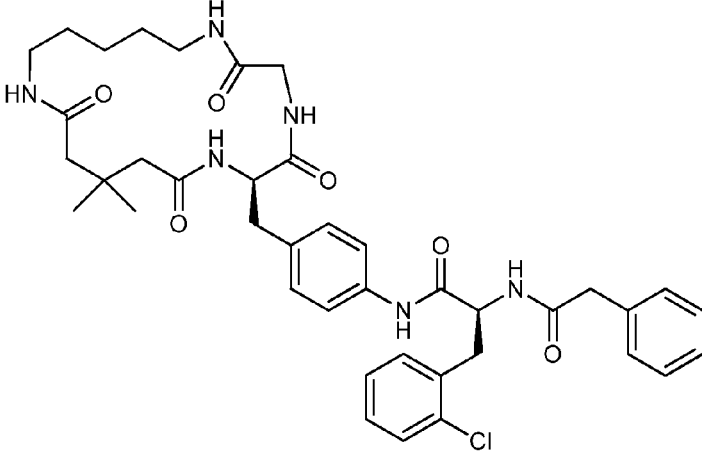
Compound No.	Structure
221	 <p>Chemical structure of Compound 221: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a long alkyl chain and a side chain containing a benzyl group, a 2-chlorophenyl group, and a benzyl group. The side chain also includes a benzyl group and a benzyl group.</p>
222	 <p>Chemical structure of Compound 222: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a long alkyl chain and a side chain containing a benzyl group, a 2-chlorophenyl group, and a benzyl group. The side chain also includes a benzyl group and a benzyl group.</p>

FIG. 12-53

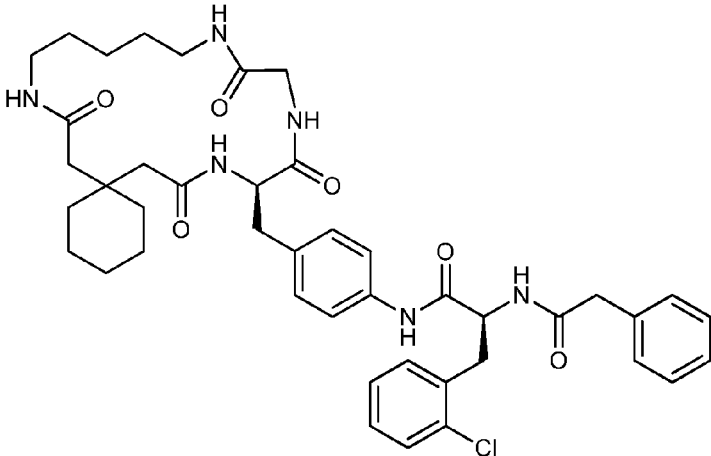
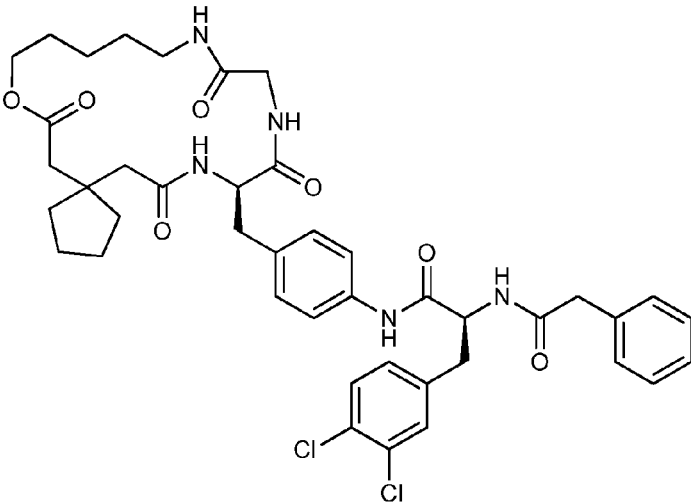
Compound No.	Structure
223	 <p>Chemical structure of Compound 223: A complex molecule featuring a bicyclic amide system (cyclohexane fused to a five-membered ring) connected via a carbonyl group to a chain containing a secondary amide, a tertiary amide, and a benzamide moiety. The benzamide is further substituted with a 2-chlorophenyl group and a benzyl group.</p>
224	 <p>Chemical structure of Compound 224: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a five-membered ring) connected via a carbonyl group to a chain containing a secondary amide, a tertiary amide, and a benzamide moiety. The benzamide is further substituted with a 3,5-dichlorophenyl group and a benzyl group.</p>

FIG. 12-54

[illegible]

FIG. 12-55

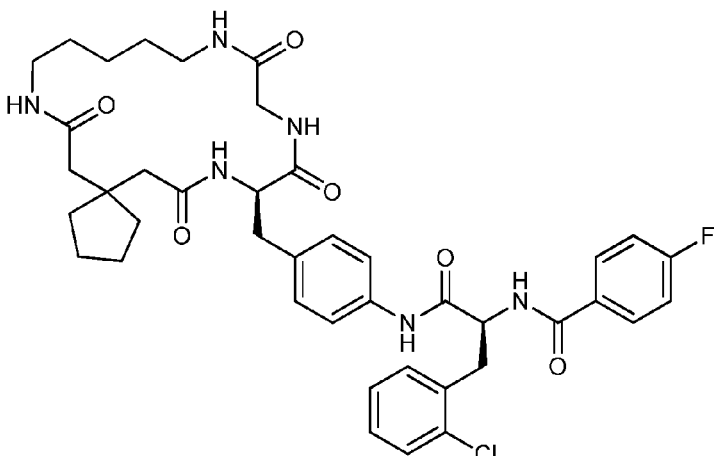
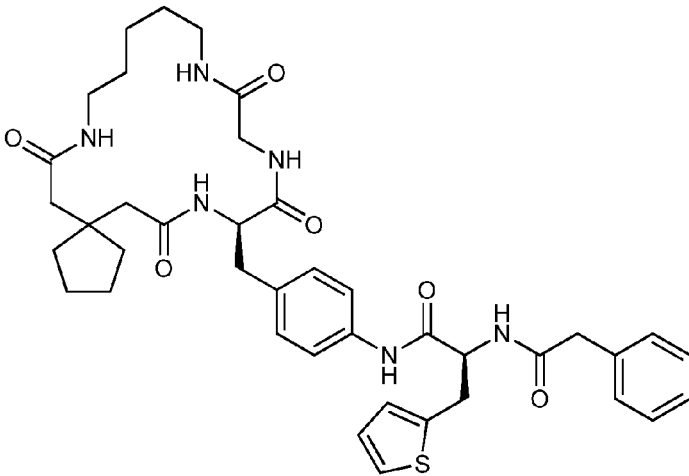
Compound No.	Structure
227	 <p>Chemical structure of Compound 227: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide and a side chain containing a benzamide moiety. The side chain includes a 4-fluorophenyl group and a 2-chlorophenyl group.</p>
228	 <p>Chemical structure of Compound 228: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide and a side chain containing a benzamide moiety. The side chain includes a thiophene ring and a phenyl group.</p>

FIG. 12-56

Compound No.	Structure
229	
230	

FIG. 12-57

Compound No.	Structure
231	
232	

FIG. 12-58

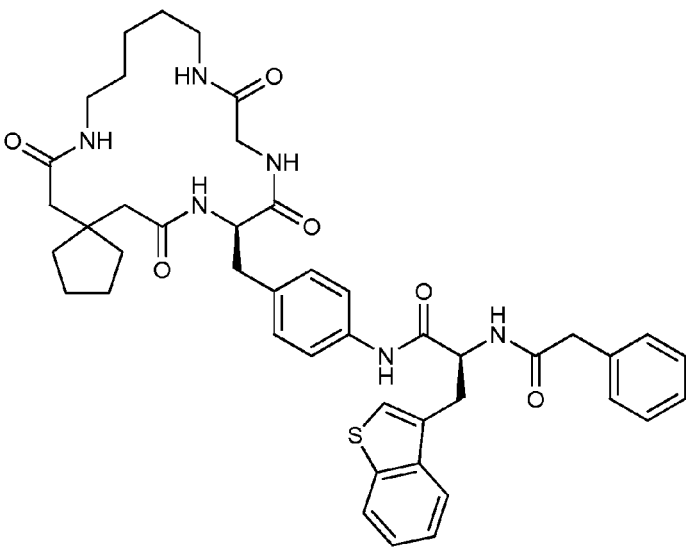
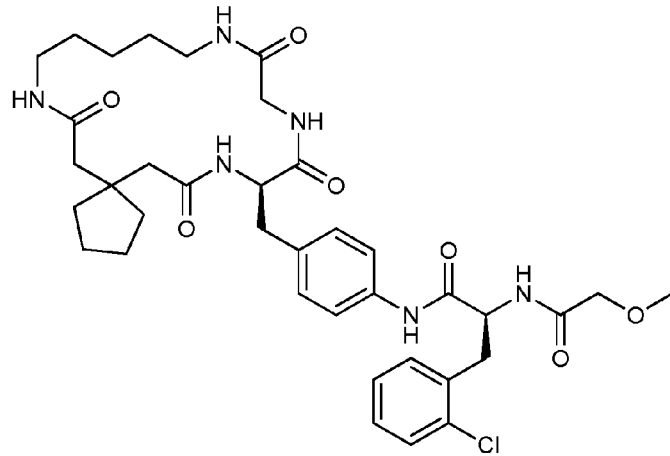
Compound No.	Structure
233	 <p>Chemical structure of Compound 233: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and carbamate groups. The chain includes a benzamide moiety, a thienobenzamide moiety, and a benzyl carbamate moiety.</p>
234	 <p>Chemical structure of Compound 234: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and carbamate groups. The chain includes a benzamide moiety, a 2-chlorobenzamide moiety, and a benzyl carbamate moiety.</p>

FIG. 12-59

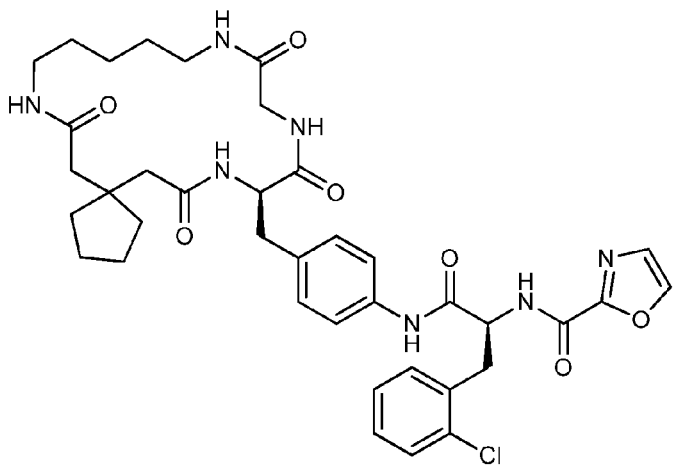
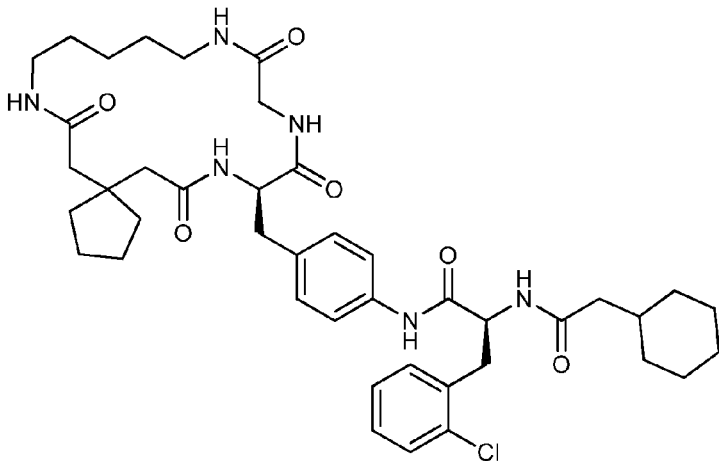
Compound No.	Structure
235	 <p>Chemical structure of Compound 235: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety linked to a 2-chlorophenyl ring, which is further connected to a chain containing an amide group and a furan ring.</p>
236	 <p>Chemical structure of Compound 236: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety linked to a 2-chlorophenyl ring, which is further connected to a chain containing an amide group and a cyclohexyl ring.</p>

FIG. 12-60

Compound No.	Structure
237	
238	

FIG. 12-61

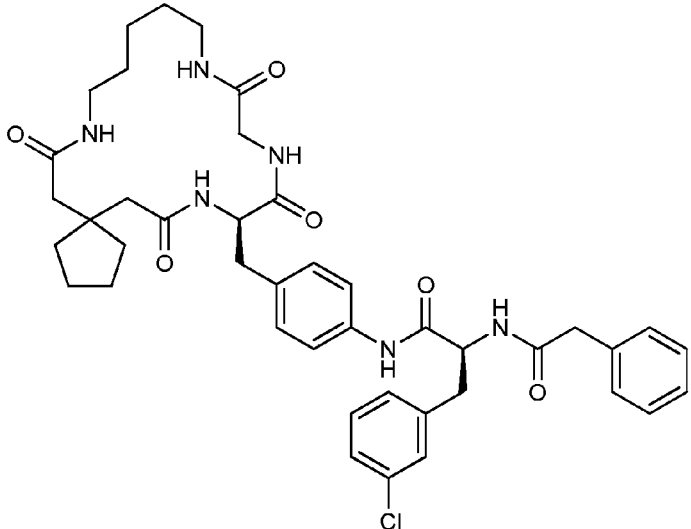
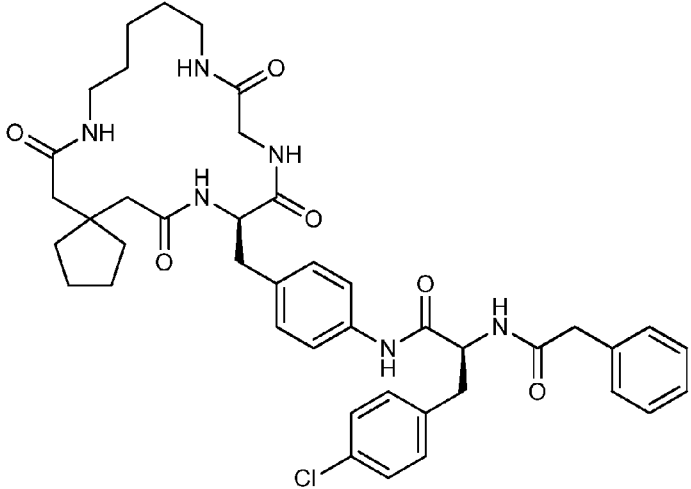
Compound No.	Structure
239	 <p>Chemical structure of Compound 239: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(amide)propan-2-yl group. This is linked via a methylene group to a 4-((4-chlorophenyl)amino)-2-oxo-1,2,3,4-tetrahydropyridine-5-yl group, which is further substituted with a 2-phenylacetamido group.</p>
240	 <p>Chemical structure of Compound 240: A complex molecule featuring a cyclopentane ring substituted with a 1,3-bis(amide)propan-2-yl group. This is linked via a methylene group to a 4-((3-chlorophenyl)amino)-2-oxo-1,2,3,4-tetrahydropyridine-5-yl group, which is further substituted with a 2-phenylacetamido group.</p>

FIG. 12-62

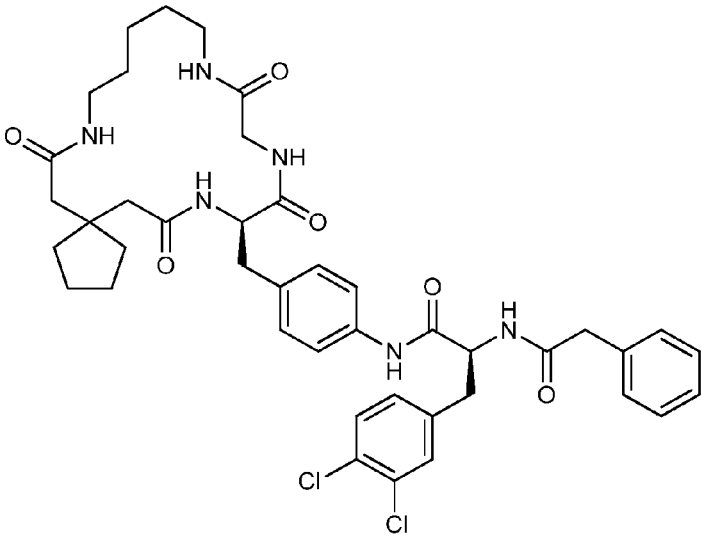
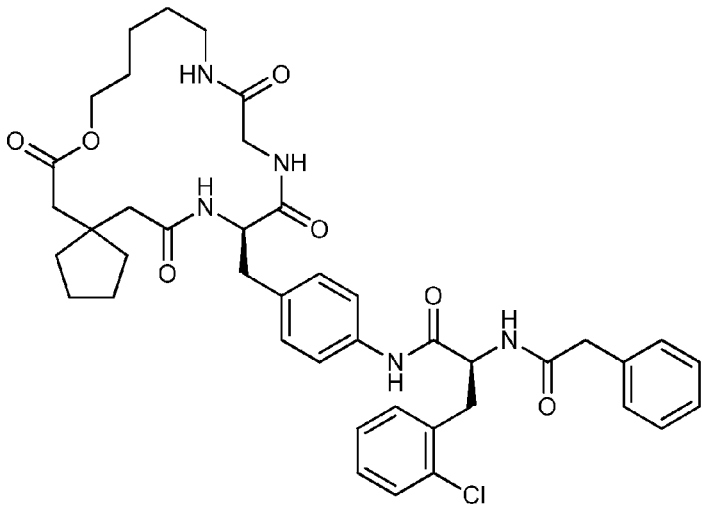
Compound No.	Structure
241	 <p>Chemical structure of Compound 241: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C(=O)-CH2-CH2-NH-C(=O)-) and a carboxylic acid group (COOH). The carboxamide group is further substituted with a benzyl group (CH2-Ph) and a 4-chlorophenyl group (CH2-Ph-Cl). The carboxylic acid group is substituted with a benzyl group (CH2-Ph).</p>
242	 <p>Chemical structure of Compound 242: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C(=O)-CH2-CH2-NH-C(=O)-) and a carboxylic acid group (COOH). The carboxamide group is further substituted with a benzyl group (CH2-Ph) and a 4-chlorophenyl group (CH2-Ph-Cl). The carboxylic acid group is substituted with a benzyl group (CH2-Ph).</p>

FIG. 12-63

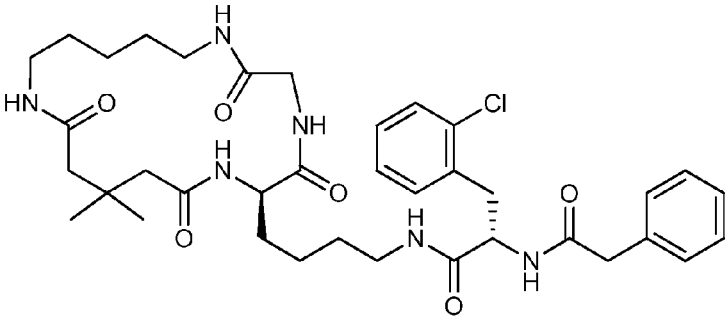
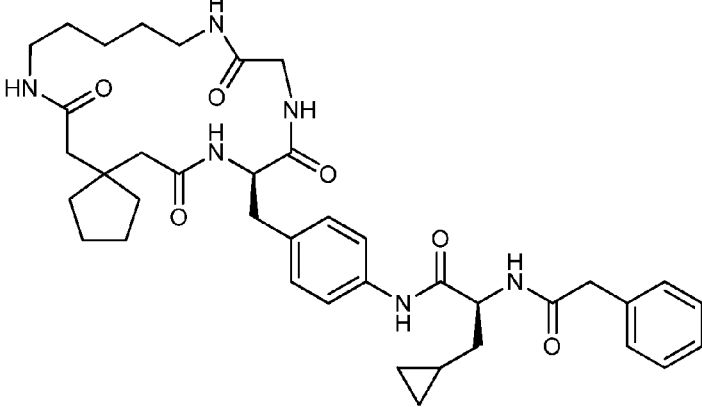
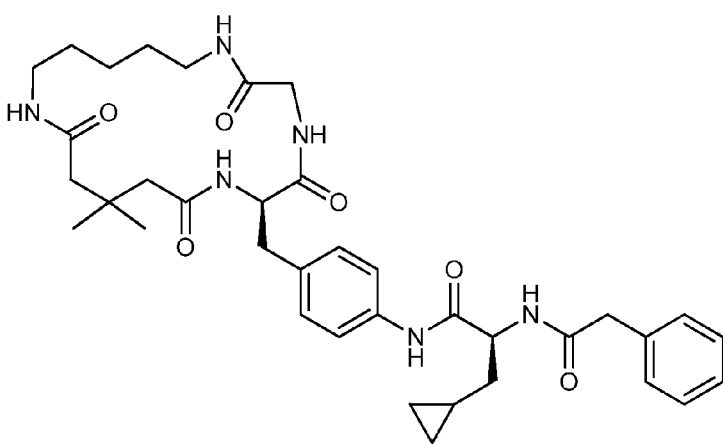
Compound No.	Structure
243	 <p>Chemical structure of Compound 243: A complex molecule featuring a central amide linkage. The left side includes a 6-membered ring with a carbonyl group and a side chain ending in a 6-membered ring with a carbonyl group. The right side includes a 6-membered ring with a carbonyl group, a side chain ending in a 6-membered ring with a carbonyl group, and a side chain ending in a 6-membered ring with a carbonyl group.</p>
244	 <p>Chemical structure of Compound 244: A complex molecule featuring a central amide linkage. The left side includes a 6-membered ring with a carbonyl group and a side chain ending in a 6-membered ring with a carbonyl group. The right side includes a 6-membered ring with a carbonyl group, a side chain ending in a 6-membered ring with a carbonyl group, and a side chain ending in a 6-membered ring with a carbonyl group.</p>
245	 <p>Chemical structure of Compound 245: A complex molecule featuring a central amide linkage. The left side includes a 6-membered ring with a carbonyl group and a side chain ending in a 6-membered ring with a carbonyl group. The right side includes a 6-membered ring with a carbonyl group, a side chain ending in a 6-membered ring with a carbonyl group, and a side chain ending in a 6-membered ring with a carbonyl group.</p>

FIG. 12-64

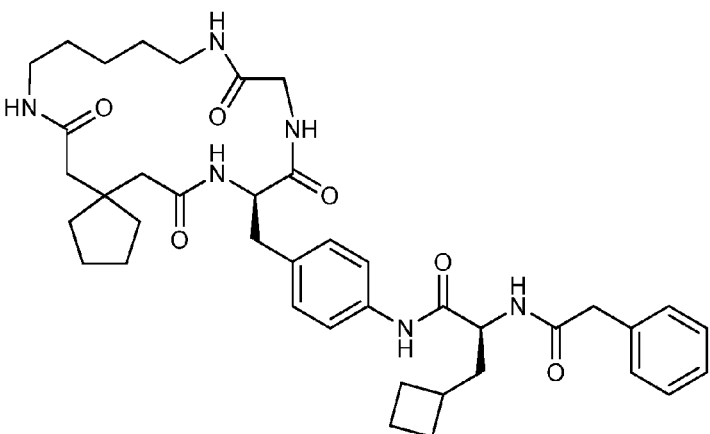
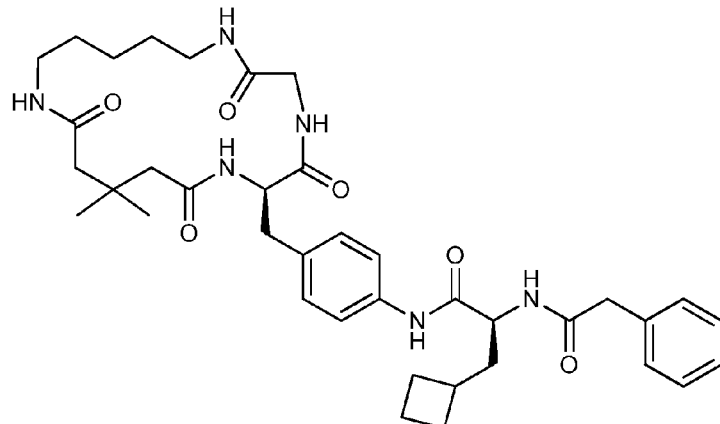
Compound No.	Structure
246	 <p>Chemical structure of Compound 246: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide and a carboxamide group. The long-chain amide is connected to a benzyl group, which is further linked to a cyclobutane ring. The cyclobutane ring is substituted with a carboxamide group and a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group.</p>
247	 <p>Chemical structure of Compound 247: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide and a carboxamide group. The long-chain amide is connected to a benzyl group, which is further linked to a cyclobutane ring. The cyclobutane ring is substituted with a carboxamide group and a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group. The benzyl group is connected to a carboxamide group, which is further linked to a benzyl group.</p>

FIG. 12-65

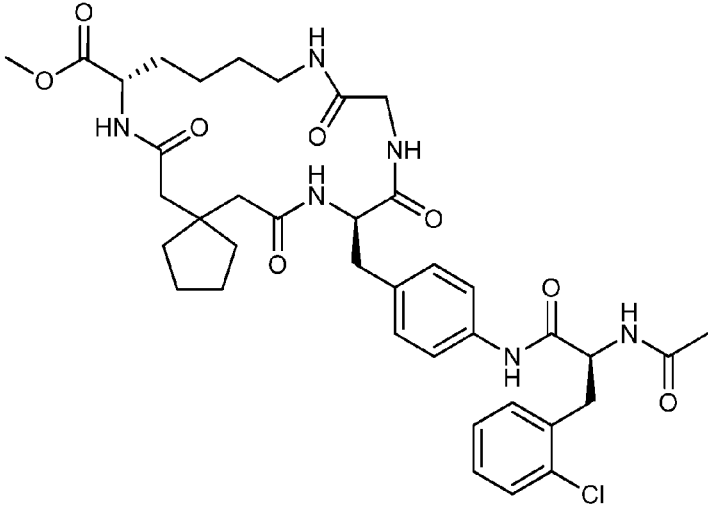
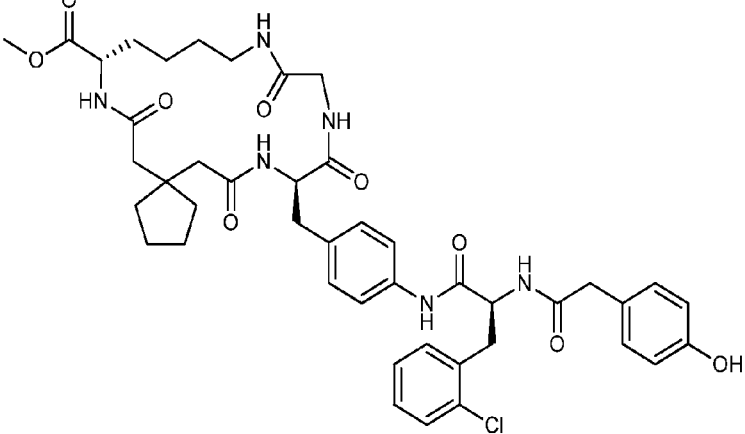
Compound No.	Structure
248	 <p>Chemical structure of Compound 248: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a dashed bond) and a methoxy group. The right side includes a 4-chlorophenyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a solid wedge bond) and an acetamido group.</p>
249	 <p>Chemical structure of Compound 249: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a dashed bond) and a methoxy group. The right side includes a 4-chlorophenyl ring connected to a carbonyl group, which is further linked to a chiral center (marked with a solid wedge bond) and a 4-hydroxyphenyl group.</p>

FIG. 12-66

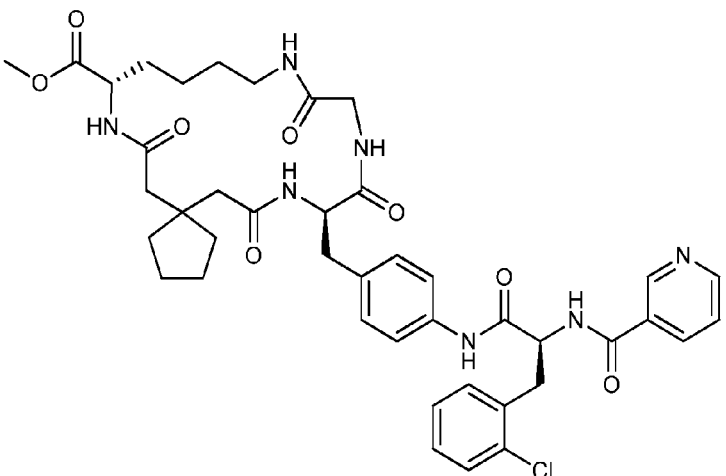
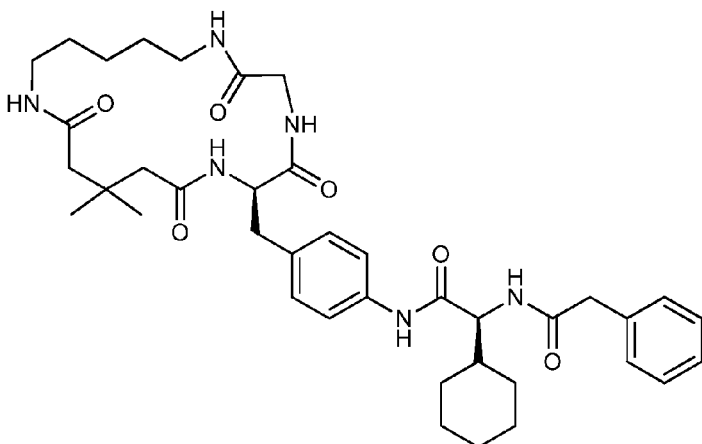
Compound No.	Structure
250	 <p>Chemical structure of Compound 250: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring and a methoxycarbonyl group. The right side includes a 4-chlorophenyl ring, a pyridine ring, and a benzamide moiety.</p>
251	 <p>Chemical structure of Compound 251: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring and a methoxycarbonyl group. The right side includes a 4-chlorophenyl ring, a pyridine ring, and a benzamide moiety.</p>

FIG. 12-67

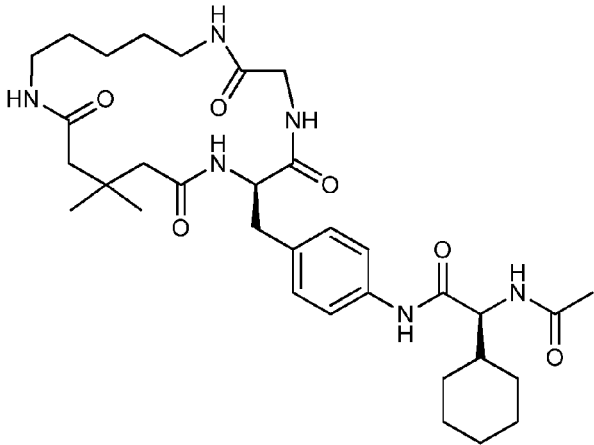
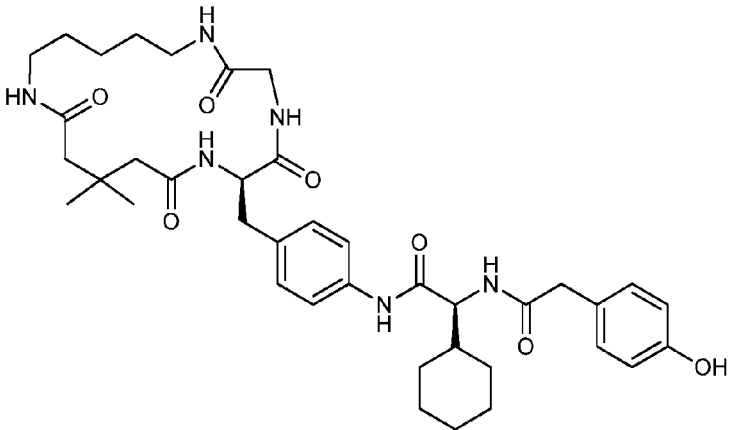
Compound No.	Structure
252	 <p>Chemical structure of Compound 252: A complex molecule featuring a central amide linkage connecting a substituted cyclohexane ring to a benzamide moiety. The benzamide is further substituted with a long-chain amide and a branched amide group. The structure includes a cyclohexane ring, a benzamide group, and a long-chain amide with a branched amide group.</p>
253	 <p>Chemical structure of Compound 253: A complex molecule featuring a central amide linkage connecting a substituted cyclohexane ring to a benzamide moiety. The benzamide is further substituted with a long-chain amide and a branched amide group. The structure includes a cyclohexane ring, a benzamide group, and a long-chain amide with a branched amide group.</p>

FIG. 12-68

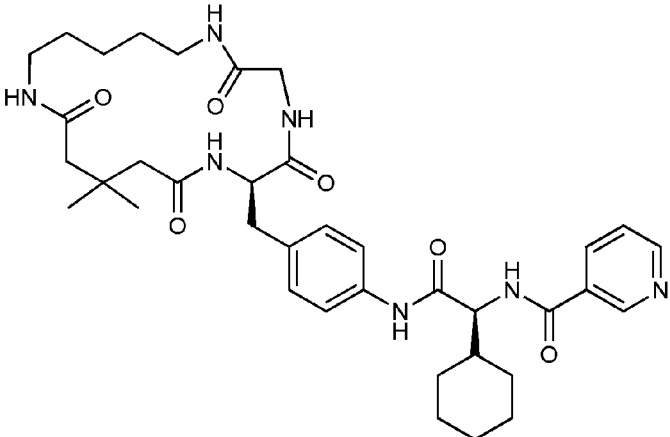
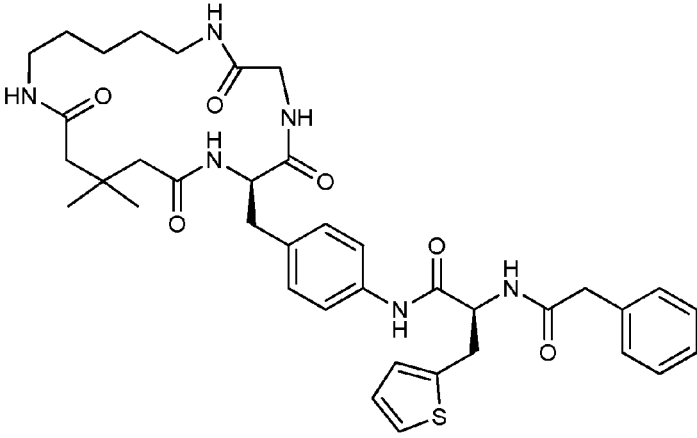
Compound No.	Structure
254	 <p>Chemical structure of Compound 254: A complex molecule featuring a central amide linkage. The left side consists of a 10-membered ring with two amide groups and a quaternary carbon. The right side is a 4-((1-cyclohexyl-2-((pyridin-4-ylamino)carbonyl)ethyl)amino)benzamide derivative.</p>
255	 <p>Chemical structure of Compound 255: A complex molecule featuring a central amide linkage. The left side is identical to Compound 254. The right side is a 4-((1-(thiophen-2-yl)-2-((benzylamino)carbonyl)ethyl)amino)benzamide derivative.</p>

FIG. 12-69

Compound No.	Structure
256	
257	

FIG. 12-70

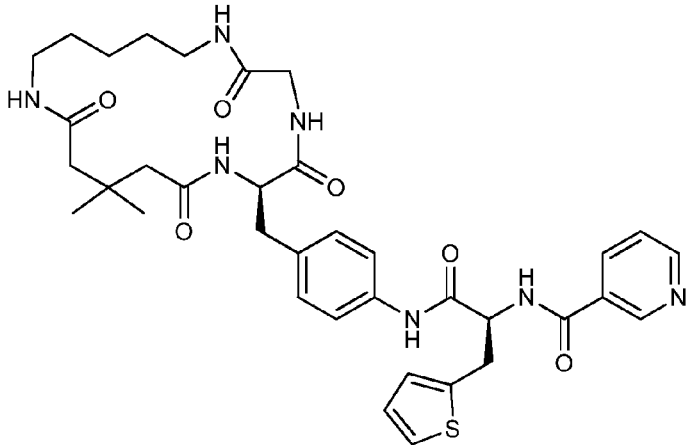
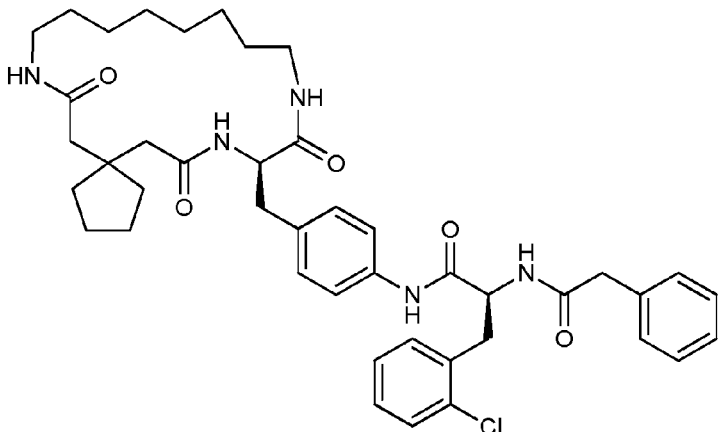
Compound No.	Structure
258	 <p>Chemical structure of Compound 258: A complex molecule featuring a central amide linkage. The left side consists of a 10-membered ring containing two amide groups and a quaternary carbon atom. The right side is a linear chain starting with a benzamide group, followed by a thiazolidine ring, and ending with a pyridine-2-carboxamide group.</p>
259	 <p>Chemical structure of Compound 259: A complex molecule featuring a central amide linkage. The left side consists of a 10-membered ring containing two amide groups and a cyclopentyl group. The right side is a linear chain starting with a benzamide group, followed by a thiazolidine ring, and ending with a 2-chlorophenyl group.</p>

FIG. 12-71

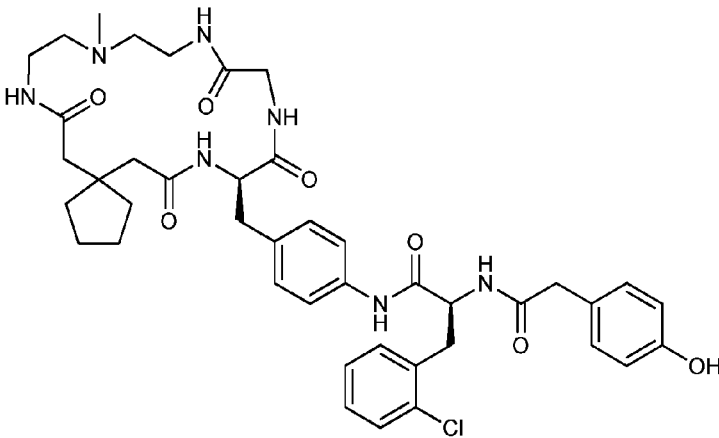
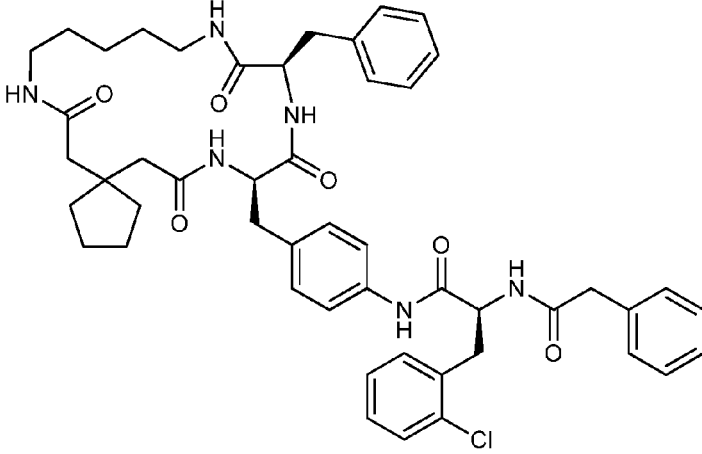
Compound No.	Structure
260	 <p>Chemical structure of Compound 260: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide structure. The right side features a benzamide moiety with a 4-hydroxyphenyl group and a 3-chlorophenyl group. The structure is highly branched and includes multiple amide and carbonyl functional groups.</p>
261	 <p>Chemical structure of Compound 261: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide structure. The right side features a benzamide moiety with a 4-phenyl group and a 3-chlorophenyl group. The structure is highly branched and includes multiple amide and carbonyl functional groups.</p>

FIG. 12-72

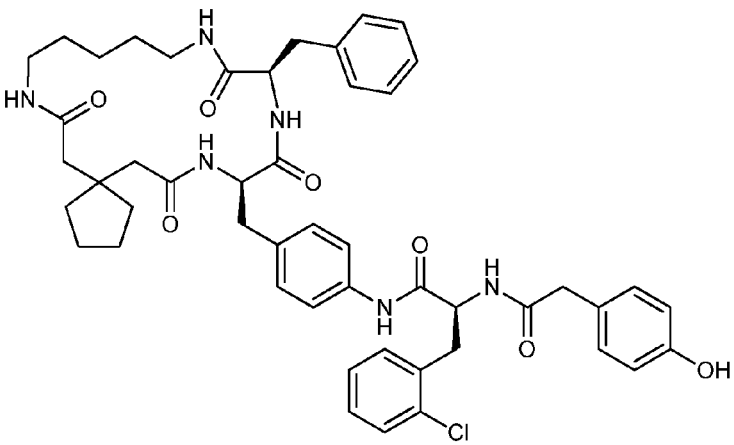
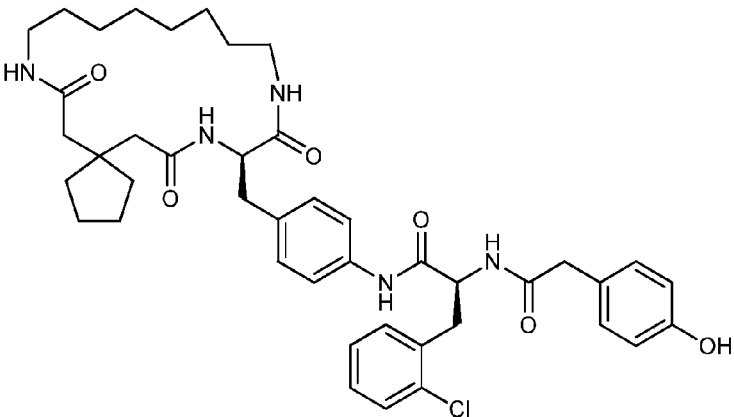
Compound No.	Structure
262	 <p>Chemical structure of Compound 262: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a long alkyl chain ending in an amide group. The right side includes a benzyl group connected to a carbonyl group, which is further linked to a long alkyl chain ending in an amide group. The central amide linkage connects the two sides.</p>
263	 <p>Chemical structure of Compound 263: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a long alkyl chain ending in an amide group. The right side includes a benzyl group connected to a carbonyl group, which is further linked to a long alkyl chain ending in an amide group. The central amide linkage connects the two sides.</p>

FIG. 12-73

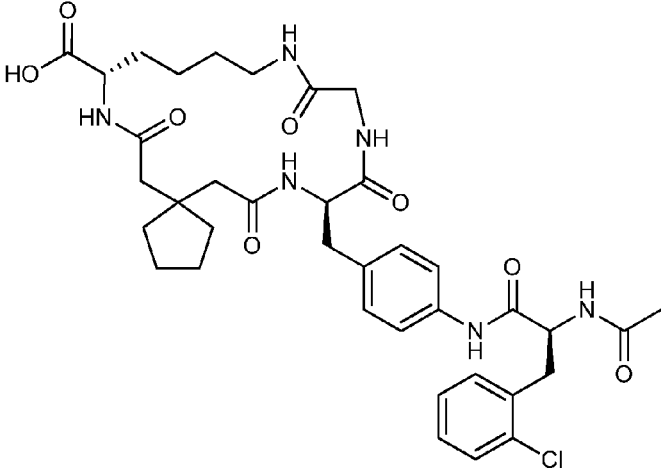
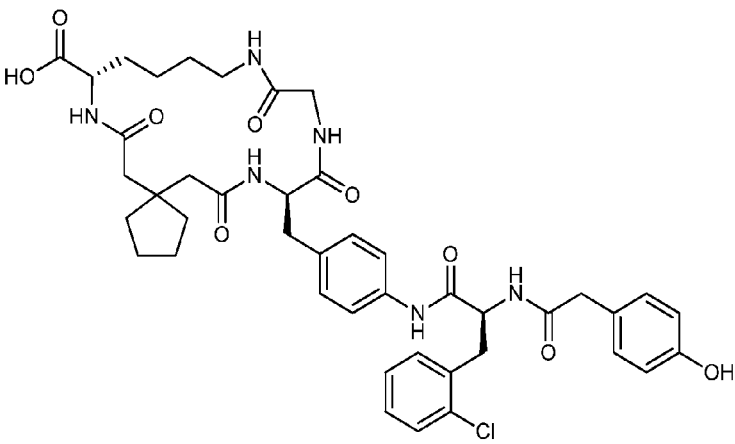
Compound No.	Structure
264	 <p>Chemical structure of Compound 264: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and an amide linkage (-NH-C(=O)-). This amide is connected to a chain containing another amide (-NH-C(=O)-) and a carbonyl group (C=O). The chain continues with a benzamide moiety (-NH-C(=O)-) and a 2-chlorophenyl group. The structure includes stereochemical indicators (wedges and dashes) for the carboxylic acid and the amide linkage.</p>
265	 <p>Chemical structure of Compound 265: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and an amide linkage (-NH-C(=O)-). This amide is connected to a chain containing another amide (-NH-C(=O)-) and a carbonyl group (C=O). The chain continues with a benzamide moiety (-NH-C(=O)-) and a 2-chlorophenyl group. The structure includes stereochemical indicators (wedges and dashes) for the carboxylic acid and the amide linkage.</p>

FIG. 12-74

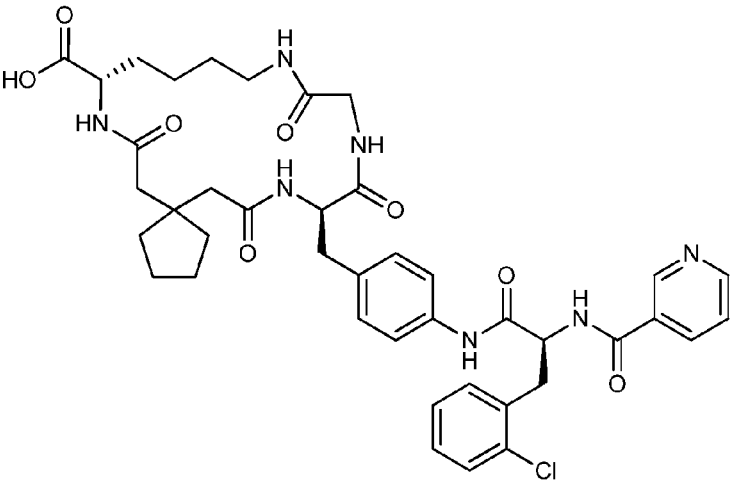
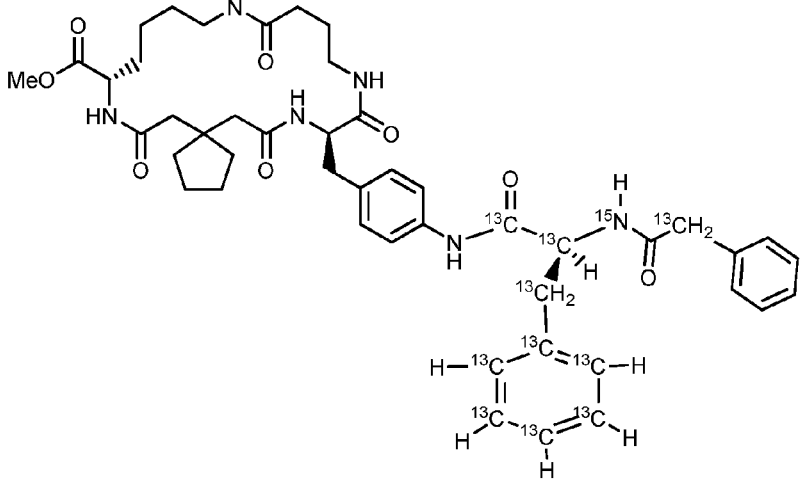
Compound No.	Structure
266	 <p>Chemical structure of Compound 266. It features a cyclopentane ring substituted with two amide groups. One amide is part of a chain ending in a carboxylic acid group (HO-C(=O)-CH2-), and the other is part of a chain ending in a pyridine ring. The structure includes a 4-chlorophenyl group and a 2-pyridyl group.</p>
267	 <p>Chemical structure of Compound 267. It features a cyclopentane ring substituted with two amide groups. One amide is part of a chain ending in a methyl ester group (MeO-C(=O)-CH2-), and the other is part of a chain ending in a 15N-labeled amide group (15N-CH2-C(=O)-). The structure includes a 4-phenyl group and a 13C-labeled pyridine ring.</p>

FIG. 12-75

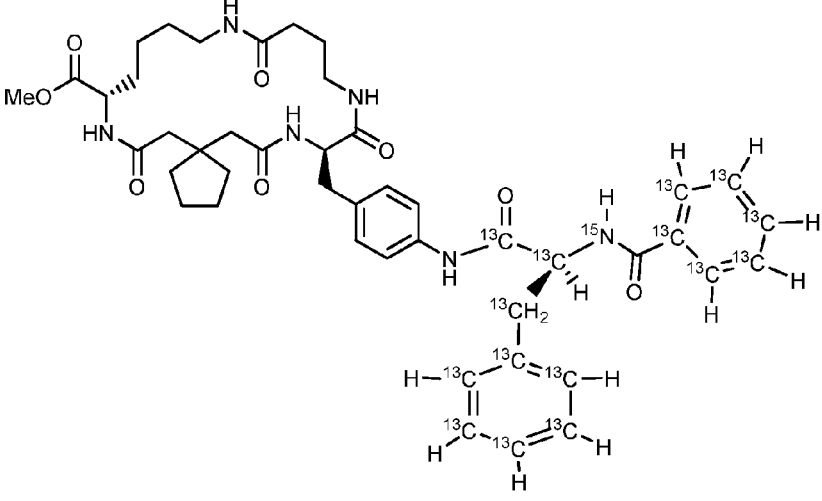
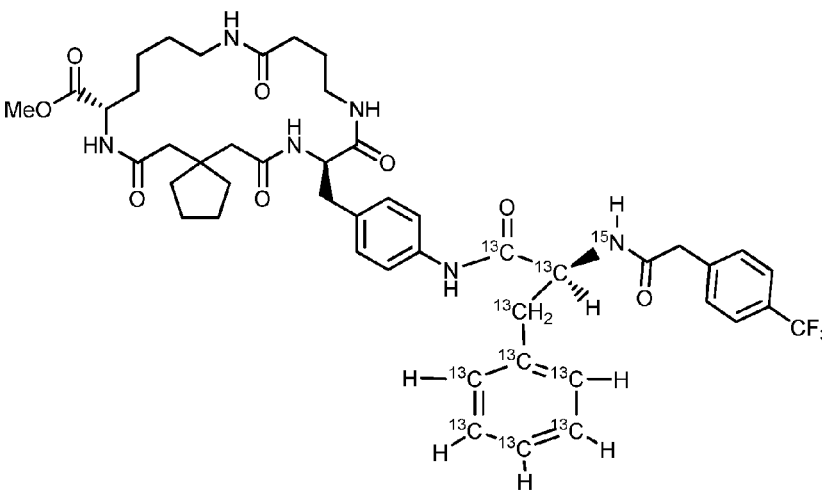
Compound No.	Structure
268	 <p>Chemical structure of Compound 268. The molecule features a complex amide backbone. On the left, a methoxy group (MeO) is attached to a carbonyl, which is part of a chain containing a cyclopentane ring. This chain is linked via an amide bond to a benzene ring. The benzene ring is further connected to a side chain containing a carbonyl group, a ^{13}C label, a ^{15}N label, and a $^{13}\text{CH}_2$ group. This side chain is connected to a pyridine ring, which is also labeled with ^{13}C and ^{15}N atoms. The pyridine ring is substituted with a $^{13}\text{CH}_2$ group and a ^{13}C label. The structure is highly symmetrical and includes multiple ^{13}C and ^{15}N labels.</p>
269	 <p>Chemical structure of Compound 269. The molecule features a complex amide backbone. On the left, a methoxy group (MeO) is attached to a carbonyl, which is part of a chain containing a cyclopentane ring. This chain is linked via an amide bond to a benzene ring. The benzene ring is further connected to a side chain containing a carbonyl group, a ^{13}C label, a ^{15}N label, and a $^{13}\text{CH}_2$ group. This side chain is connected to a pyridine ring, which is also labeled with ^{13}C and ^{15}N atoms. The pyridine ring is substituted with a $^{13}\text{CH}_2$ group and a ^{13}C label. The structure is highly symmetrical and includes multiple ^{13}C and ^{15}N labels.</p>

FIG. 12-76

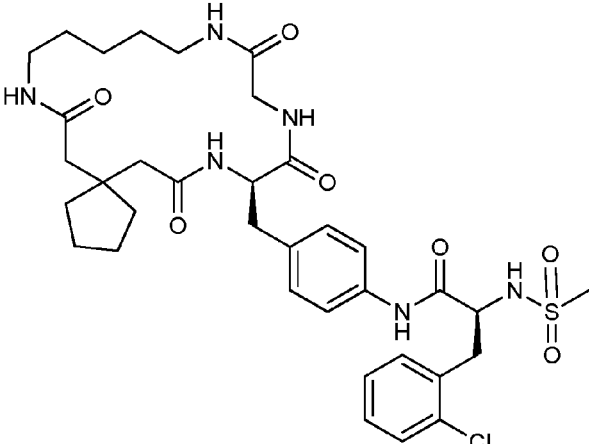
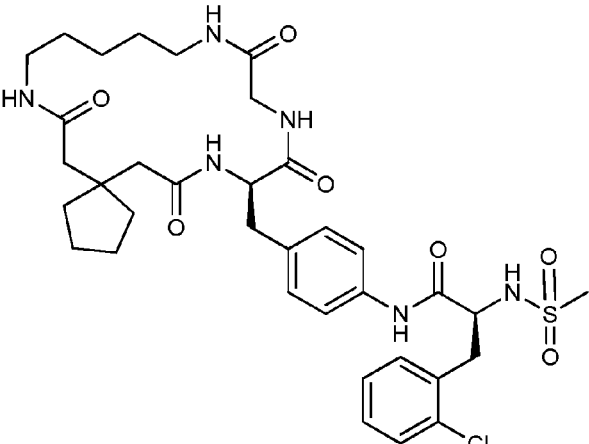
Compound No.	Structure
270	 <p>The chemical structure of compound 270 is a complex molecule featuring a central amide linkage. On the left, a cyclopentyl ring is attached to a chain containing two amide groups and a long alkyl chain. On the right, a 2-chlorophenyl ring is attached to a chain containing an amide group and a sulfonamide group. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms.</p>
270	 <p>The chemical structure of compound 270 is identical to the one in the first row, showing a complex molecule with a central amide linkage, a cyclopentyl ring, a 2-chlorophenyl ring, and a sulfonamide group. The structure is drawn in a perspective view, showing the spatial arrangement of the atoms.</p>

FIG. 12-77

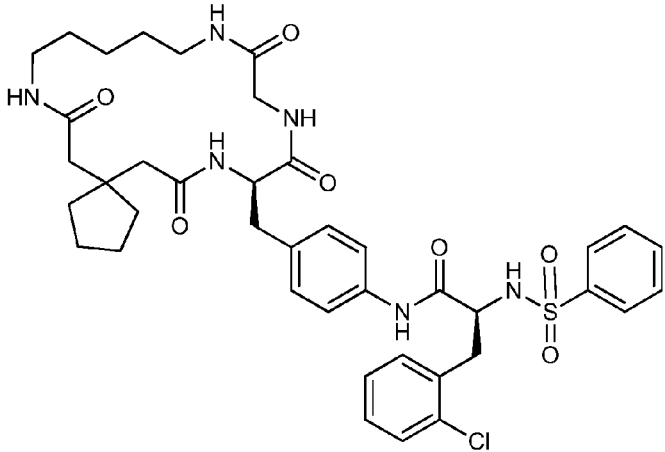
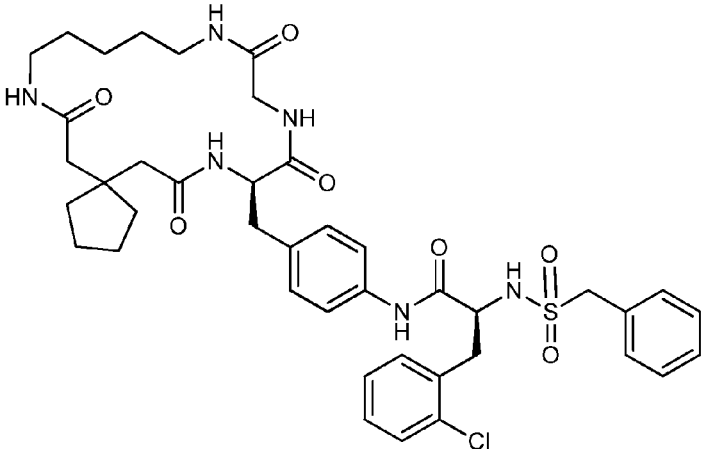
Compound No.	Structure
271	 <p>Chemical structure of Compound 271: A complex molecule featuring a cyclopentyl ring substituted with a long-chain amide group (HN-C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-CH2-NH-C(=O)-CH2-). This amide chain is further substituted with a 4-(2-chlorophenyl)-2-phenyl-2-sulfonyl-1,3-dioxane-5-carboxamide moiety. The structure includes a benzene ring with a chlorine atom at the 2-position, a 1,3-dioxane ring, and a sulfonamide group (NH-SO2-Ph).</p>
272	 <p>Chemical structure of Compound 272: A complex molecule featuring a cyclopentyl ring substituted with a long-chain amide group (HN-C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-CH2-NH-C(=O)-CH2-). This amide chain is further substituted with a 4-(2-chlorophenyl)-2-phenyl-2-sulfonyl-1,3-dioxane-5-carboxamide moiety. The structure includes a benzene ring with a chlorine atom at the 2-position, a 1,3-dioxane ring, and a sulfonamide group (NH-SO2-CH2-Ph).</p>

FIG. 12-78

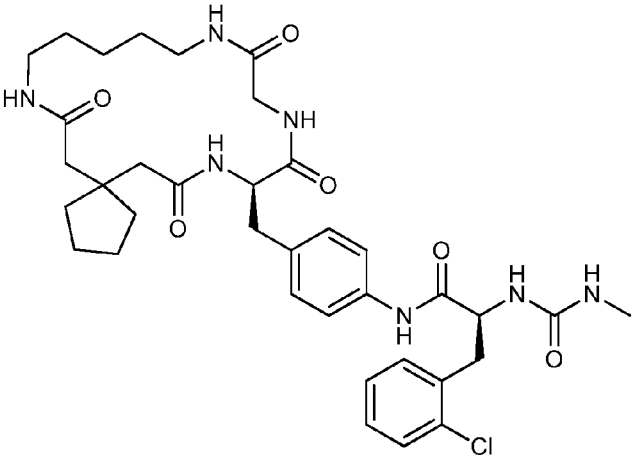
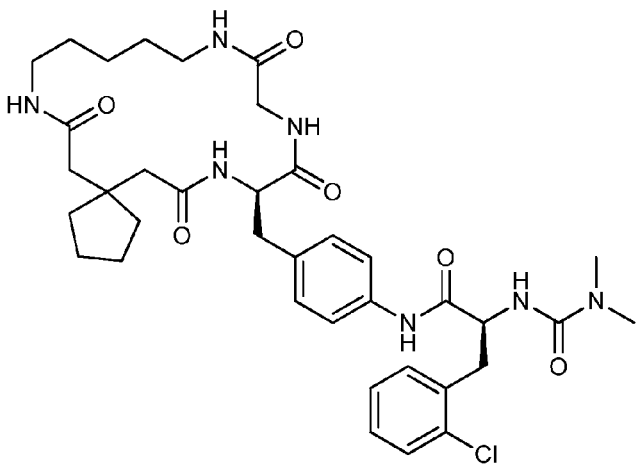
Compound No.	Structure
273	 <p>Chemical structure of compound 273. It features a 1,4-bis(amide)pentane chain. One amide is attached to a 1-cyclopentyl-2-oxoethyl group. The other amide is attached to a 1-((2-chlorophenyl)amino)-2-oxoethyl group. The central amide is attached to a 1-((4-((2-chlorophenyl)amino)-2-oxoethyl)phenyl)ethyl group.</p>
274	 <p>Chemical structure of compound 274. It is identical to compound 273, featuring a 1,4-bis(amide)pentane chain with a 1-cyclopentyl-2-oxoethyl group, a 1-((2-chlorophenyl)amino)-2-oxoethyl group, and a 1-((4-((2-chlorophenyl)amino)-2-oxoethyl)phenyl)ethyl group.</p>

FIG. 12-79

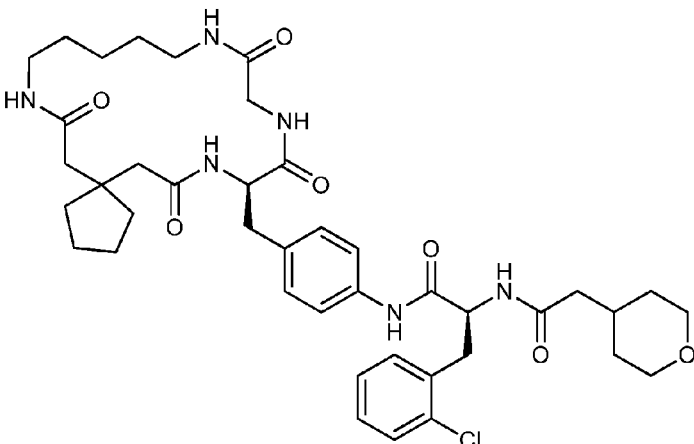
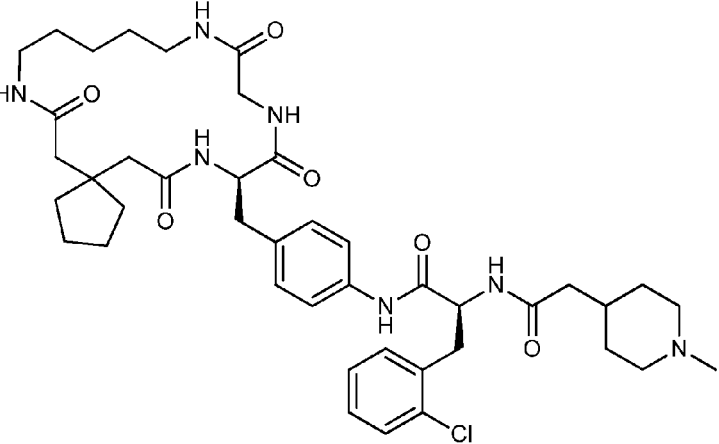
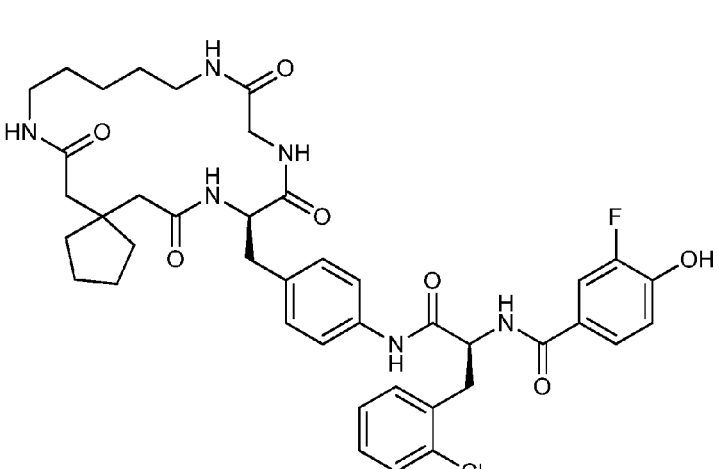
Compound No.	Structure
275	 <p>Chemical structure of compound 275: A complex molecule featuring a central benzene ring substituted with a 2-chlorophenyl group and a 4-(2-chlorophenyl)phenyl group. The 4-(2-chlorophenyl)phenyl group is further substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group.</p>
276	 <p>Chemical structure of compound 276: A complex molecule featuring a central benzene ring substituted with a 2-chlorophenyl group and a 4-(2-chlorophenyl)phenyl group. The 4-(2-chlorophenyl)phenyl group is further substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group.</p>
277	 <p>Chemical structure of compound 277: A complex molecule featuring a central benzene ring substituted with a 2-chlorophenyl group and a 4-(2-chlorophenyl)phenyl group. The 4-(2-chlorophenyl)phenyl group is further substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group. The 2-chlorophenyl group is substituted with a 2-(2-chlorophenyl)ethyl group.</p>

FIG. 12-80

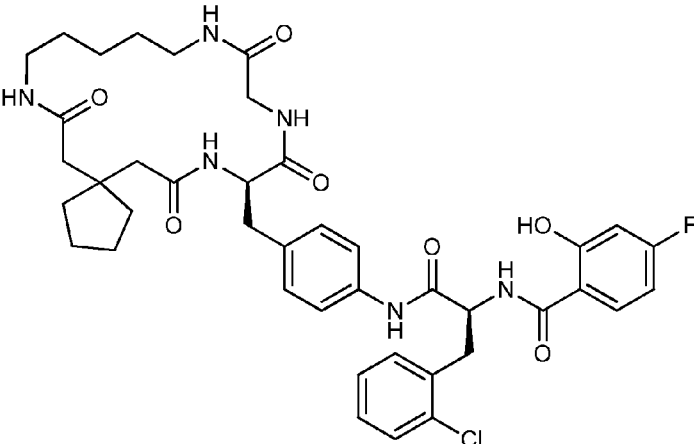
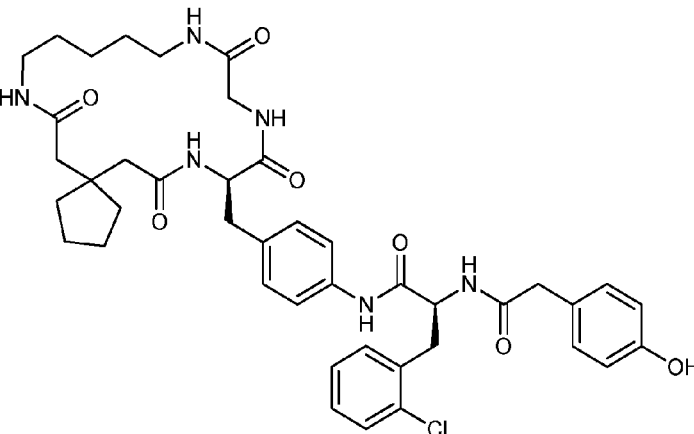
Compound No.	Structure
278	 <p>Chemical structure of Compound 278: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety with a 4-fluorophenyl group and a 2-chlorophenyl group.</p>
279	 <p>Chemical structure of Compound 279: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentyl ring attached to a chain containing two amide groups and a long alkyl chain. The right side features a benzamide moiety with a 4-hydroxyphenyl group and a 2-chlorophenyl group.</p>

FIG. 12-81

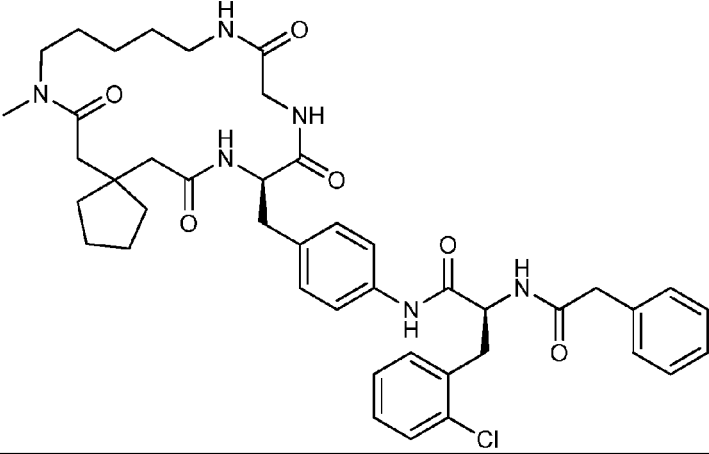
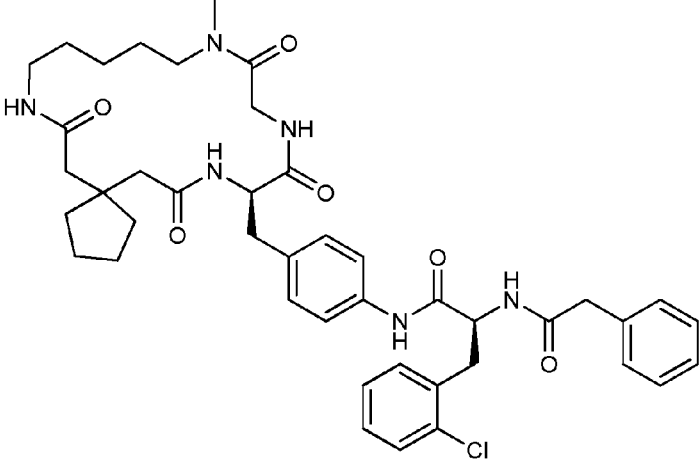
Compound No.	Structure
280	 <p>Chemical structure of Compound 280: A complex molecule featuring a central amide linkage. The left side consists of a 6-membered ring with a carbonyl group and a methyl group on the nitrogen. The right side is a 4-chlorophenyl group connected to a 2-phenyl-2-oxoethyl group, which is further connected to a 2-phenyl-2-oxoethyl group via an amide linkage.</p>
281	 <p>Chemical structure of Compound 281: A complex molecule featuring a central amide linkage. The left side consists of a 6-membered ring with a carbonyl group and a methyl group on the nitrogen. The right side is a 4-chlorophenyl group connected to a 2-phenyl-2-oxoethyl group, which is further connected to a 2-phenyl-2-oxoethyl group via an amide linkage.</p>

FIG. 12-82

Compound No.	Structure
282	
283	

FIG. 12-83

Compound No.	Structure
284	
285	

FIG. 12-84

Compound No.	Structure
286	
288	

FIG. 12-85

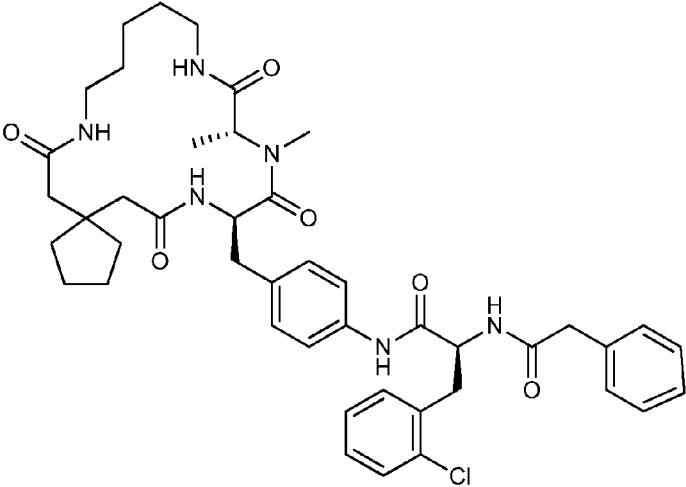
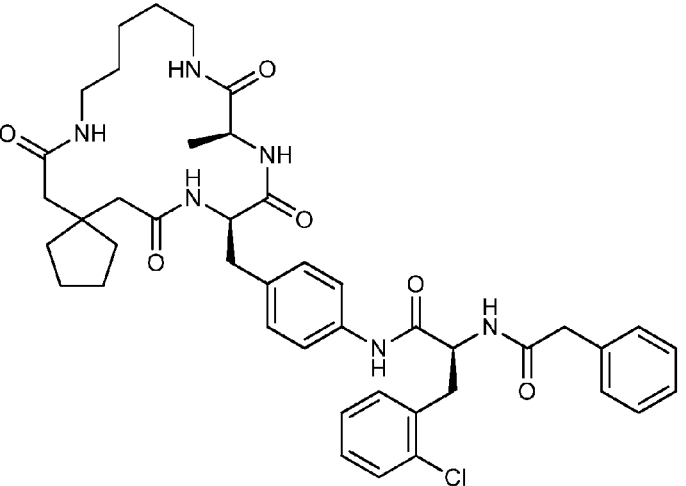
Compound No.	Structure
289	 <p>Chemical structure of Compound 289. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via an amide bond to a chiral center (indicated by a dashed bond). This chiral center is further linked to a benzene ring, which is connected to another amide group. This amide group is linked to a chiral center (indicated by a solid wedge bond), which is connected to a benzene ring with a chlorine substituent. Finally, this chiral center is linked to an amide group, which is connected to a benzene ring.</p>
290	 <p>Chemical structure of Compound 290. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via an amide bond to a chiral center (indicated by a solid wedge bond). This chiral center is further linked to a benzene ring, which is connected to another amide group. This amide group is linked to a chiral center (indicated by a solid wedge bond), which is connected to a benzene ring with a chlorine substituent. Finally, this chiral center is linked to an amide group, which is connected to a benzene ring.</p>

FIG. 12-86

Compound No.	Structure
291	
292	

FIG. 12-87

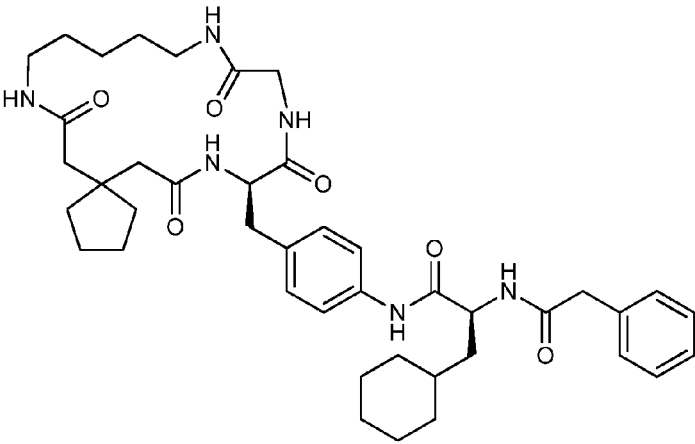
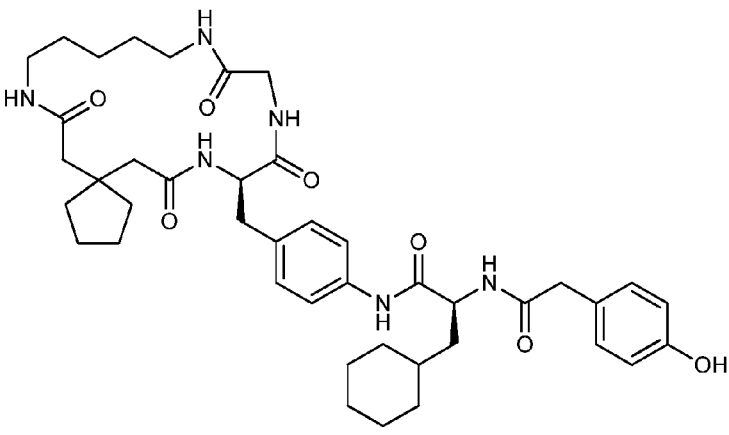
Compound No.	Structure
293	 <p>Chemical structure of Compound 293: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzene ring, which is further connected to a cyclohexane ring. The cyclohexane ring is substituted with an amide group and a side chain ending in a benzamide moiety.</p>
294	 <p>Chemical structure of Compound 294: Similar to Compound 293, but the terminal benzamide group is replaced by a 4-hydroxybenzamide moiety, indicated by the presence of an -OH group on the benzene ring.</p>

FIG. 12-88

[illegible]

FIG. 12-89

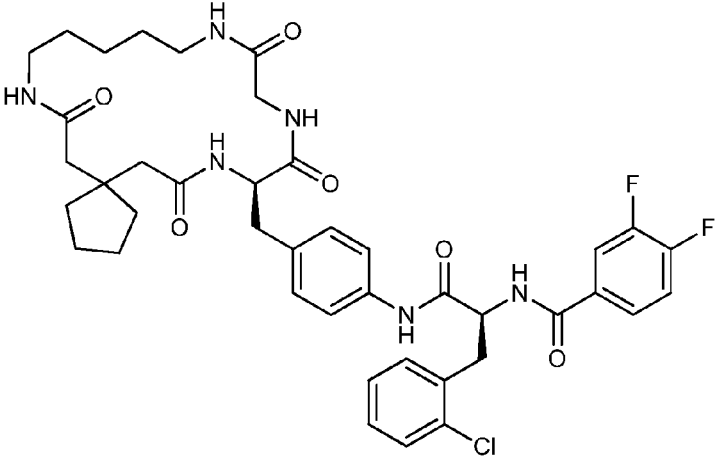
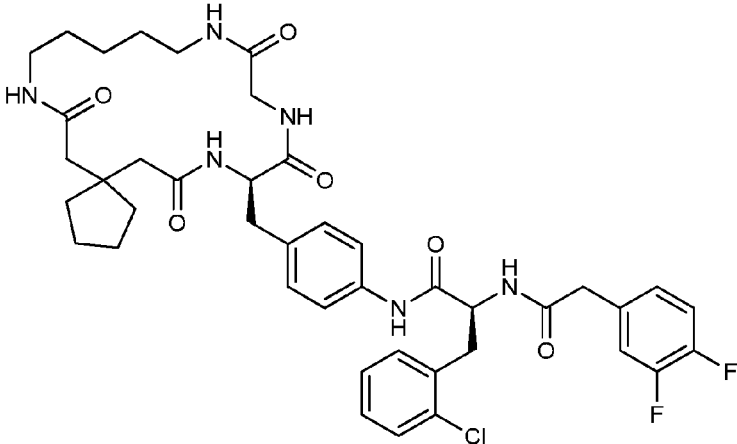
Compound No.	Structure
297	 <p>Chemical structure of Compound 297: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a five-membered amide ring) connected via a linker to a benzamide moiety. This benzamide is further linked to a 2-chlorophenyl group, which is connected to a 2-(2-chlorophenyl)-2-oxoethyl group. The final part of the molecule is a 2-(2,4-difluorophenyl)-2-oxoethyl group.</p>
298	 <p>Chemical structure of Compound 298: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a five-membered amide ring) connected via a linker to a benzamide moiety. This benzamide is further linked to a 2-chlorophenyl group, which is connected to a 2-(2-chlorophenyl)-2-oxoethyl group. The final part of the molecule is a 2-(2,4-difluorophenyl)-2-oxoethyl group.</p>

FIG. 12-90

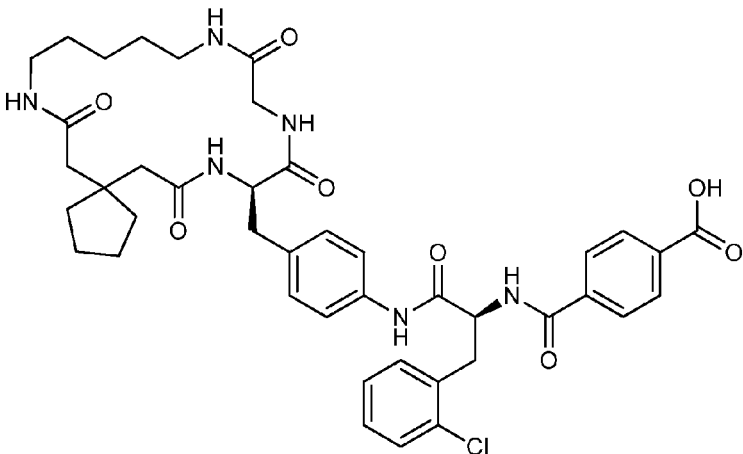
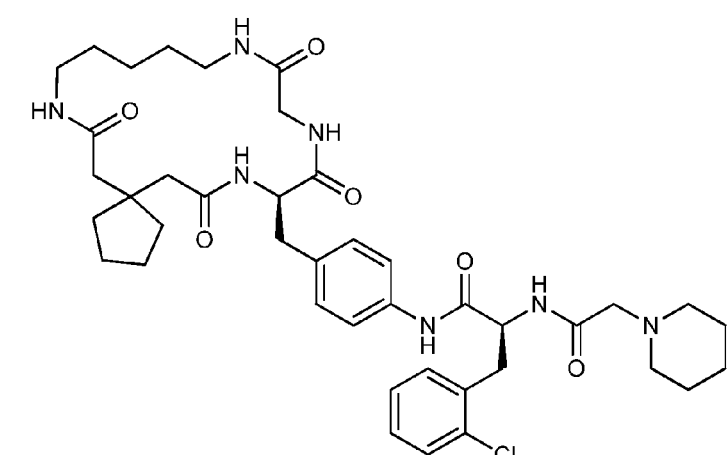
Compound No.	Structure
299	 <p>Chemical structure of Compound 299: A complex molecule featuring a central 2-chlorophenyl ring. This ring is connected via a methylene group to a 2-aminobenzamide moiety. The amide nitrogen of this moiety is linked to a 4-phenyl-2-aminopropanoate derivative. This propanoate is further connected to a cyclopentylmethyl group, which is part of a larger chain containing a 6-aminohexanoate moiety. The chain terminates in a carboxylic acid group.</p>
300	 <p>Chemical structure of Compound 300: A complex molecule featuring a central 2-chlorophenyl ring. This ring is connected via a methylene group to a 2-aminobenzamide moiety. The amide nitrogen of this moiety is linked to a 4-phenyl-2-aminopropanoate derivative. This propanoate is further connected to a cyclopentylmethyl group, which is part of a larger chain containing a 6-aminohexanoate moiety. The chain terminates in a carboxylic acid group.</p>

FIG. 12-91

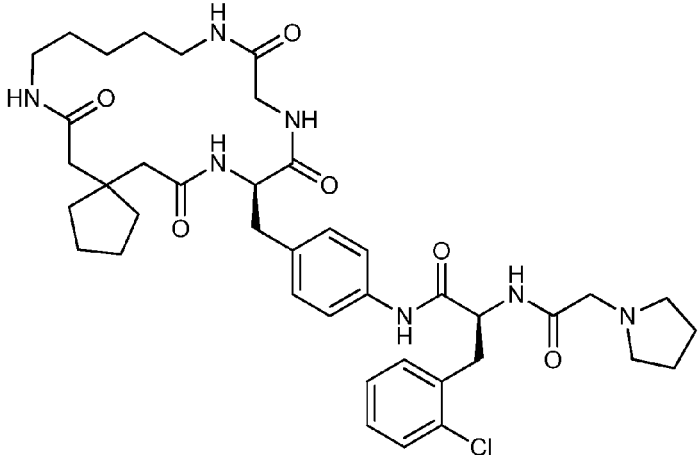
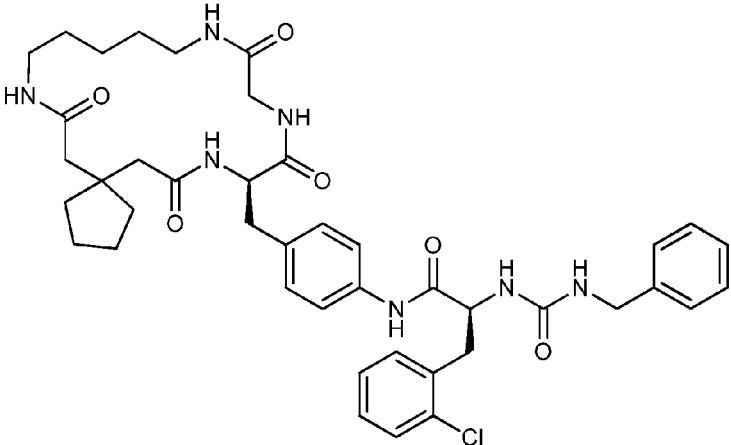
Compound No.	Structure
301	 <p>Chemical structure of Compound 301: A complex molecule featuring a central cyclopentane ring substituted with a long-chain amide (HN-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-CH2-), a carboxamide group (NH-C(=O)-CH2-), and a side chain containing a benzamide moiety (NH-C(=O)-CH2-phenyl-), a 2-chlorophenyl group, and a pyrrolidine ring.</p>
302	 <p>Chemical structure of Compound 302: A complex molecule featuring a central cyclopentane ring substituted with a long-chain amide (HN-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-CH2-), a carboxamide group (NH-C(=O)-CH2-), and a side chain containing a benzamide moiety (NH-C(=O)-CH2-phenyl-), a 2-chlorophenyl group, and a benzamide moiety (NH-C(=O)-CH2-phenyl-).</p>

FIG. 12-92

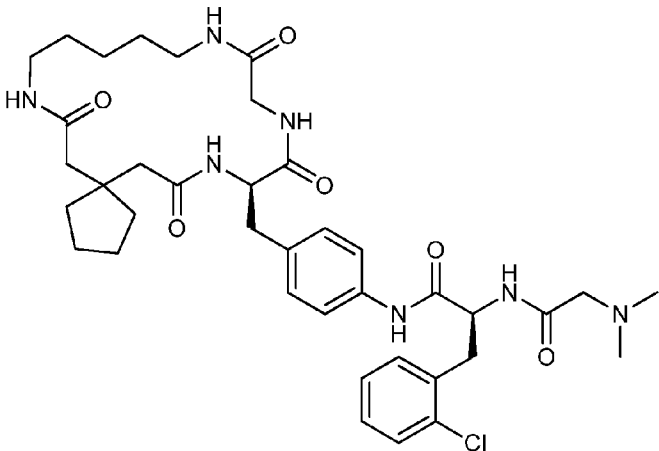
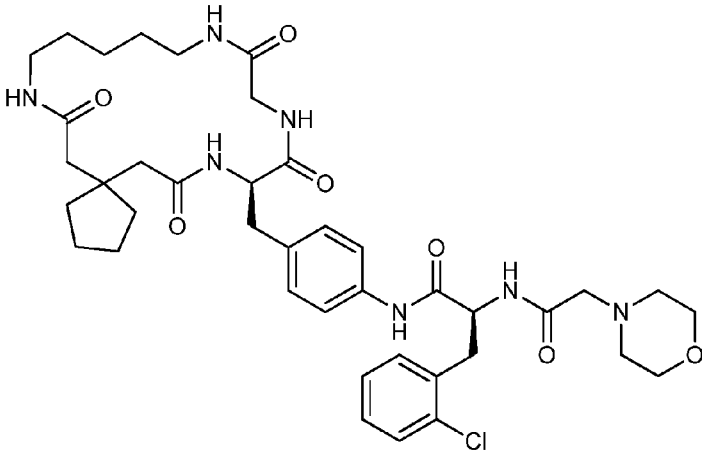
Compound No.	Structure
303	 <p>Chemical structure of Compound 303: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a five-membered amide ring) connected via a linker to a benzamide moiety. The benzamide is further connected to a 2-chlorophenyl group, which is linked to a dimethylamino group.</p>
304	 <p>Chemical structure of Compound 304: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a five-membered amide ring) connected via a linker to a benzamide moiety. The benzamide is further connected to a 2-chlorophenyl group, which is linked to a morpholine group.</p>

FIG. 12-93

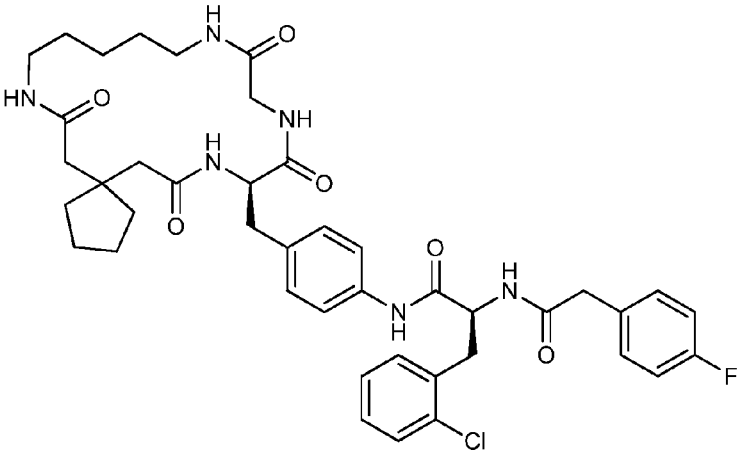
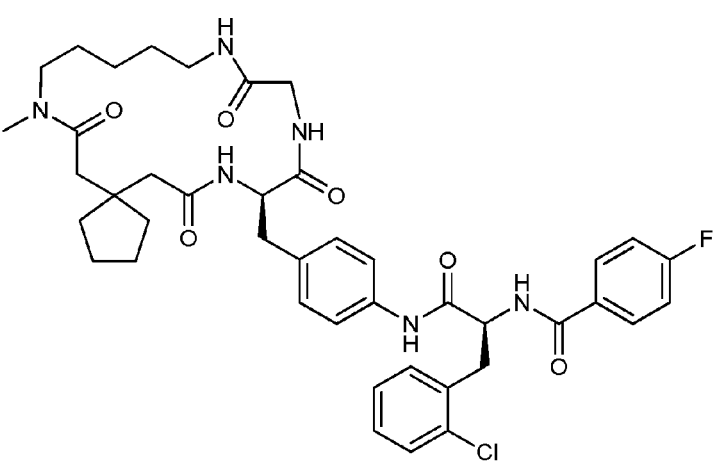
Compound No.	Structure
305	 <p>Chemical structure of Compound 305: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and ester linkages. The chain includes a 4-chlorophenyl group and a 4-fluorophenyl group. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>
306	 <p>Chemical structure of Compound 306: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and ester linkages. The chain includes a 4-chlorophenyl group and a 4-fluorophenyl group. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>

FIG. 12-94

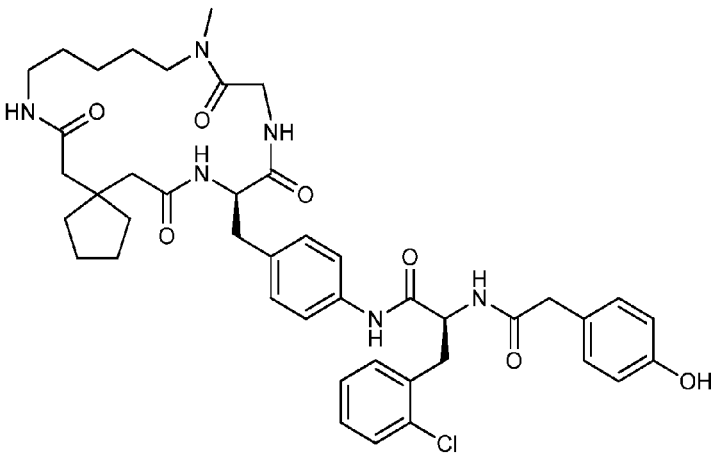
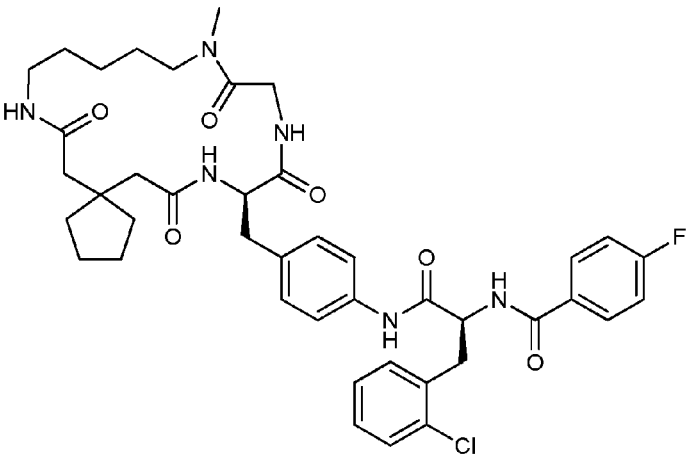
Compound No.	Structure
307	 <p>Chemical structure of Compound 307: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a carbonyl and a nitrogen atom). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a chiral center that is part of a six-membered ring containing a carbonyl and a nitrogen atom. This six-membered ring is also linked to a chiral center that is part of a benzamide moiety, which is finally connected to a 4-hydroxybenzamide group.</p>
308	 <p>Chemical structure of Compound 308: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a carbonyl and a nitrogen atom). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a chiral center that is part of a six-membered ring containing a carbonyl and a nitrogen atom. This six-membered ring is also linked to a chiral center that is part of a benzamide moiety, which is finally connected to a 4-fluorobenzamide group.</p>

FIG. 12-95

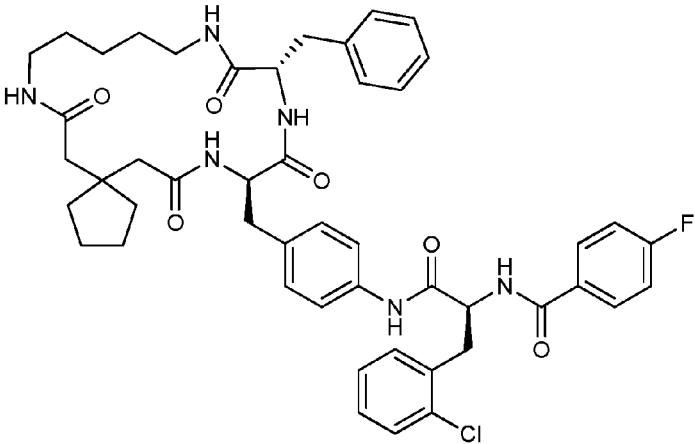
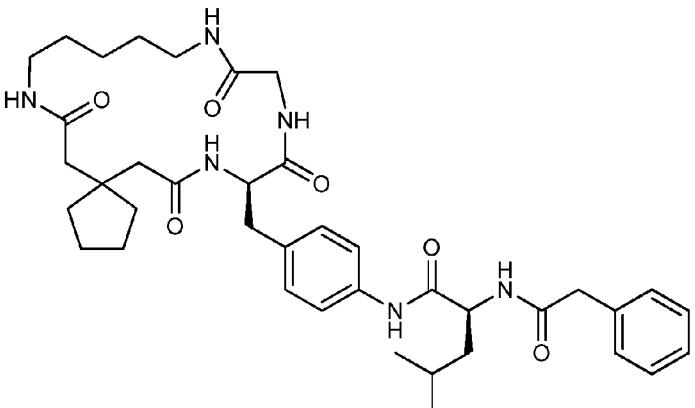
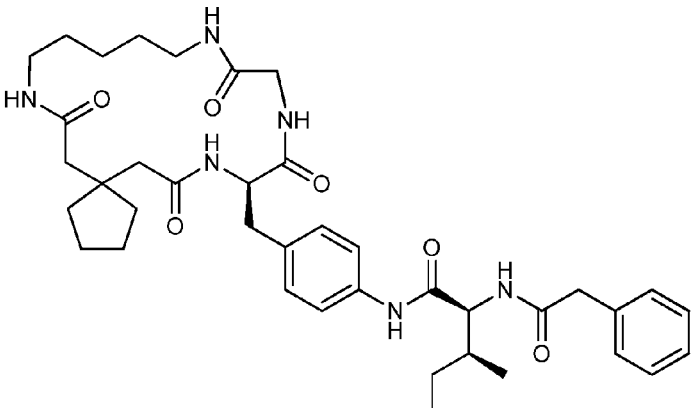
Compound No.	Structure
309	 <p>Chemical structure of Compound 309: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a chain with a terminal amide group (HN) and a carbonyl group (C=O). The right side includes a benzyl group (CH2-Ph) connected to a chain with a terminal amide group (NH) and a carbonyl group (C=O). The central amide linkage connects the two chains. The right chain also features a 4-fluorophenyl group (Ph-F) and a 2-chlorophenyl group (Ph-Cl).</p>
310	 <p>Chemical structure of Compound 310: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a chain with a terminal amide group (HN) and a carbonyl group (C=O). The right side includes a benzyl group (CH2-Ph) connected to a chain with a terminal amide group (NH) and a carbonyl group (C=O). The central amide linkage connects the two chains. The right chain also features a 4-phenyl group (Ph) and a 2-phenyl group (Ph).</p>
311	 <p>Chemical structure of Compound 311: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a chain with a terminal amide group (HN) and a carbonyl group (C=O). The right side includes a benzyl group (CH2-Ph) connected to a chain with a terminal amide group (NH) and a carbonyl group (C=O). The central amide linkage connects the two chains. The right chain also features a 4-phenyl group (Ph) and a 2-phenyl group (Ph).</p>

FIG. 12-96

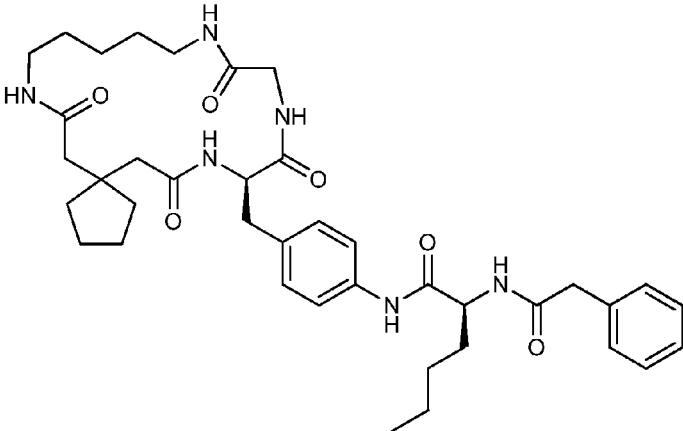
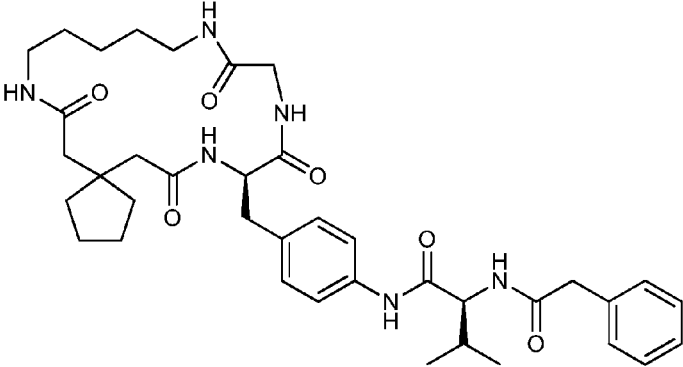
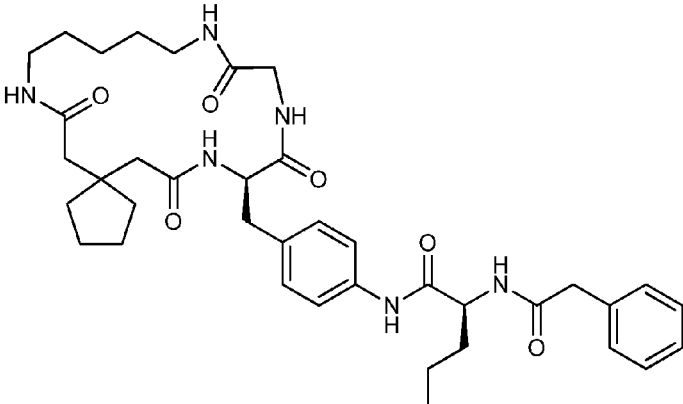
Compound No.	Structure
312	 <p>Chemical structure of compound 312. It features a cyclopentane ring substituted with a 6-oxoheptan-1-ylideneamino group and a 2-((4-((S)-1-((S)-1-phenylpropanamido)propanamido)phenyl)propanamido)propanamido group.</p>
313	 <p>Chemical structure of compound 313. It features a cyclopentane ring substituted with a 6-oxoheptan-1-ylideneamino group and a 2-((4-((S)-1-((S)-1-isobutylamido)propanamido)phenyl)propanamido)propanamido group.</p>
314	 <p>Chemical structure of compound 314. It features a cyclopentane ring substituted with a 6-oxoheptan-1-ylideneamino group and a 2-((4-((S)-1-((S)-1-propylamido)propanamido)phenyl)propanamido)propanamido group.</p>

FIG. 12-97

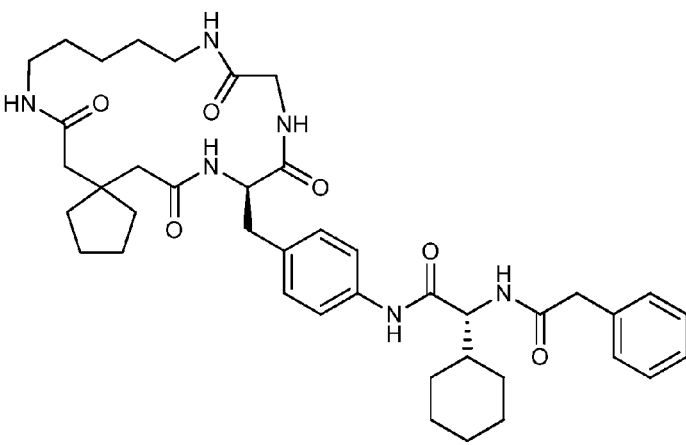
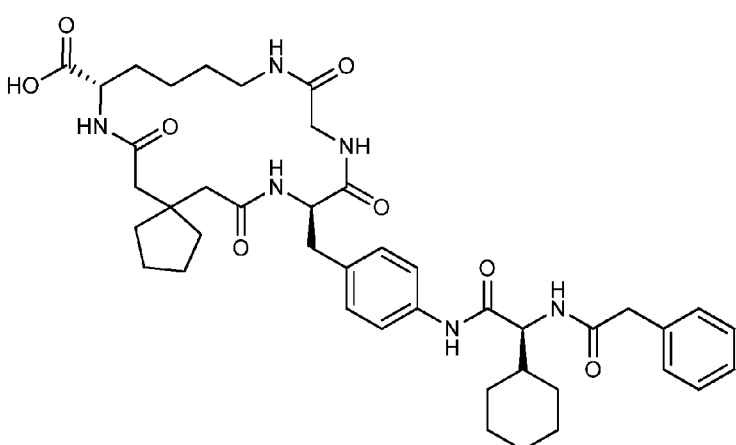
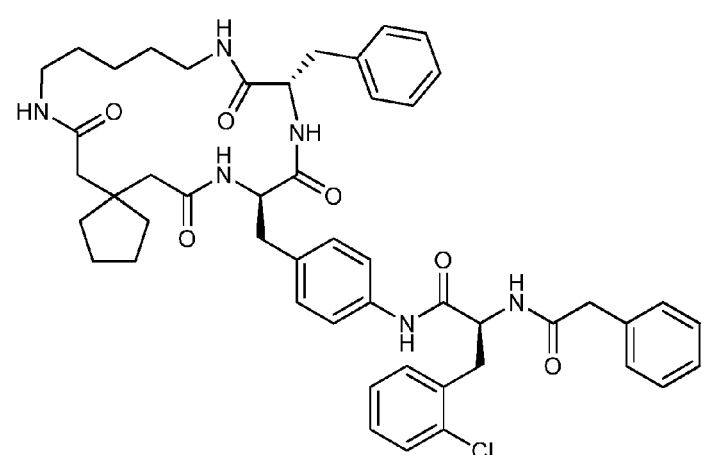
Compound No.	Structure
315	 <p>Chemical structure of Compound 315: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a cyclohexyl group and a benzyl amide group.</p>
316	 <p>Chemical structure of Compound 316: Similar to Compound 315, but the terminal amide group is replaced by a carboxylic acid group (HO-C(=O)-). The rest of the molecule, including the bicyclic amide and the benzamide-benzyl amide chain, remains the same.</p>
317	 <p>Chemical structure of Compound 317: Similar to Compound 315, but the benzamide moiety is replaced by a benzyl amide group. Additionally, the benzyl amide group is linked to a chiral center that is part of a 2-chlorophenyl amide system.</p>

FIG. 12-98

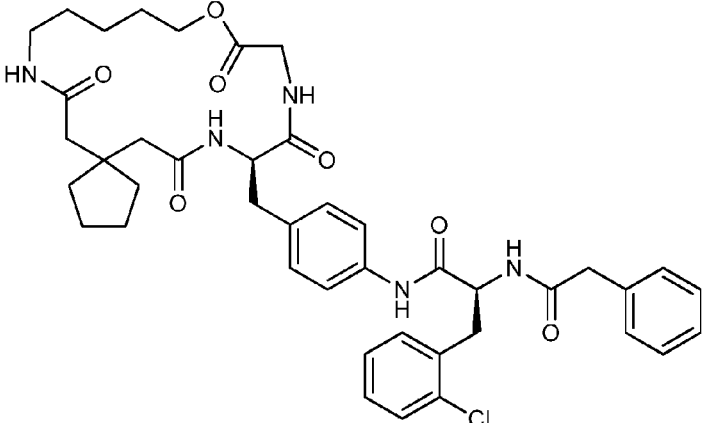
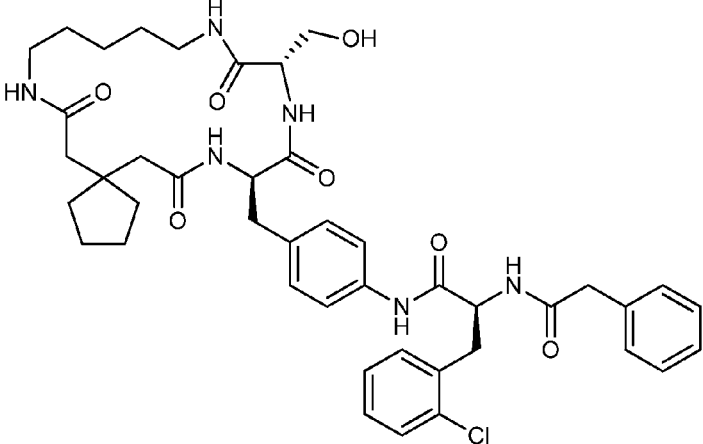
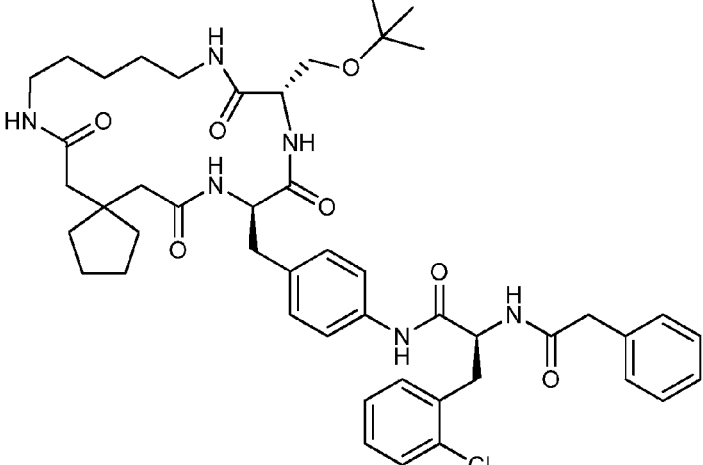
Compound No.	Structure
318	 <p>Chemical structure of Compound 318: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide groups. The chain is further substituted with a 4-phenyl group, a 2-chlorophenyl group, and a benzyl group. The structure includes a long aliphatic chain with an amide group and a cyclopentyl ring.</p>
319	 <p>Chemical structure of Compound 319: Similar to Compound 318, but the long aliphatic chain is replaced by a shorter chain ending in a hydroxyl group (OH).</p>
320	 <p>Chemical structure of Compound 320: Similar to Compound 318, but the long aliphatic chain is replaced by a shorter chain ending in a tert-butoxy group (OC(CH₃)₃).</p>

FIG. 12-99

Compound No.	Structure
321	
322	

FIG. 12-100

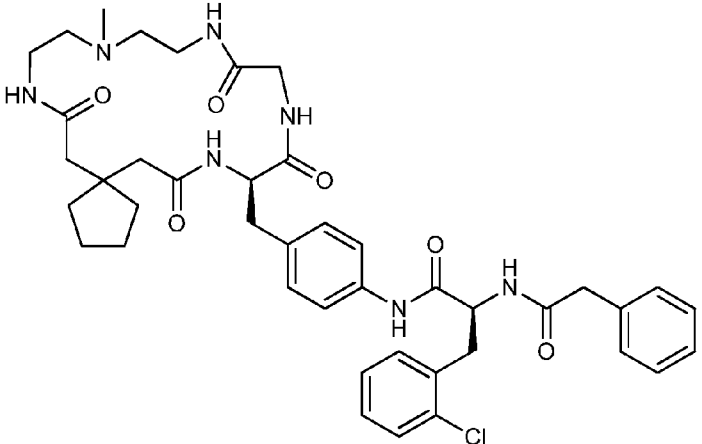
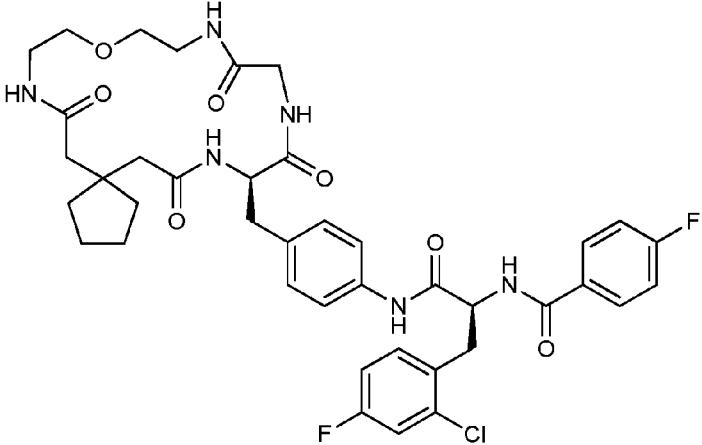
Compound No.	Structure
323	 <p>Chemical structure of Compound 323: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a five-membered amide ring) connected via a carbonyl group to a chiral center. This chiral center is further connected to a benzyl group, which is linked to a benzamide moiety. The benzamide moiety is connected to a chiral center that is part of a six-membered amide ring. This six-membered amide ring is further connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring. The final chiral center is connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring. The final chiral center is connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring.</p>
324	 <p>Chemical structure of Compound 324: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a five-membered amide ring) connected via a carbonyl group to a chiral center. This chiral center is further connected to a benzyl group, which is linked to a benzamide moiety. The benzamide moiety is connected to a chiral center that is part of a six-membered amide ring. This six-membered amide ring is further connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring. The final chiral center is connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring. The final chiral center is connected to a benzamide moiety, which is linked to a chiral center that is part of a six-membered amide ring.</p>

FIG. 12-101

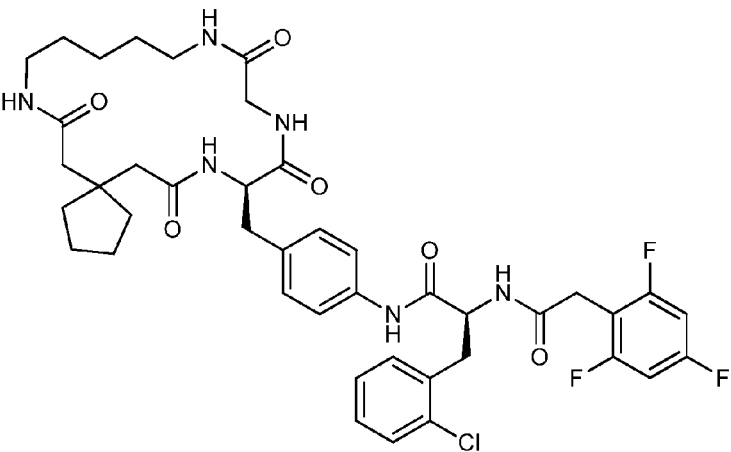
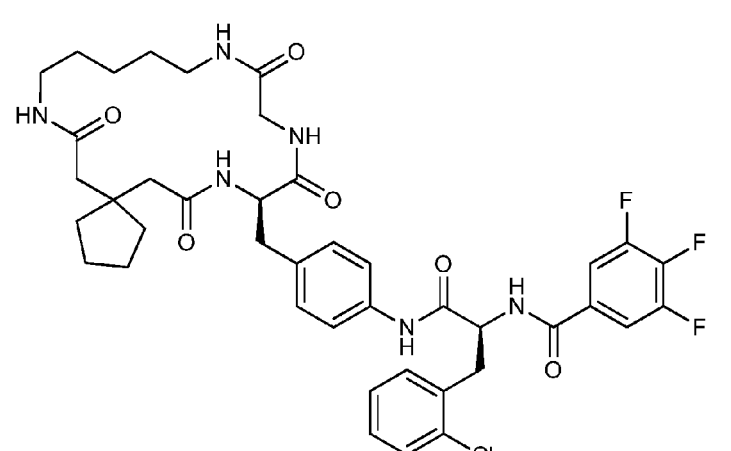
Compound No.	Structure
325	 <p>Chemical structure of Compound 325: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and ester groups. The chain includes a 4-chlorophenyl ring and a 2,4,6-trifluorophenyl ring. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>
326	 <p>Chemical structure of Compound 326: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and ester groups. The chain includes a 4-chlorophenyl ring and a 2,4,6-trifluorophenyl ring. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>

FIG. 12-102

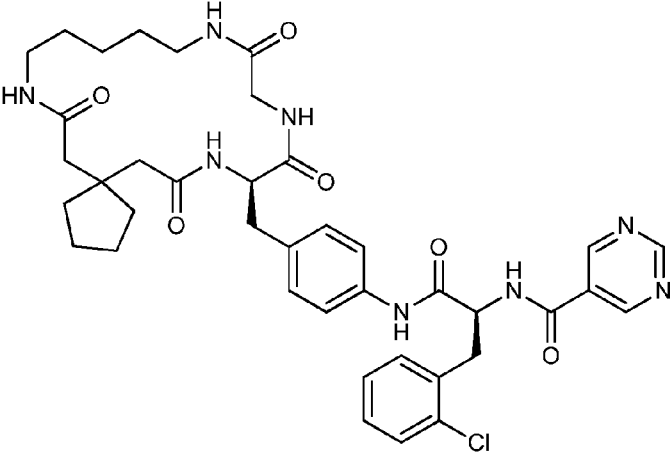
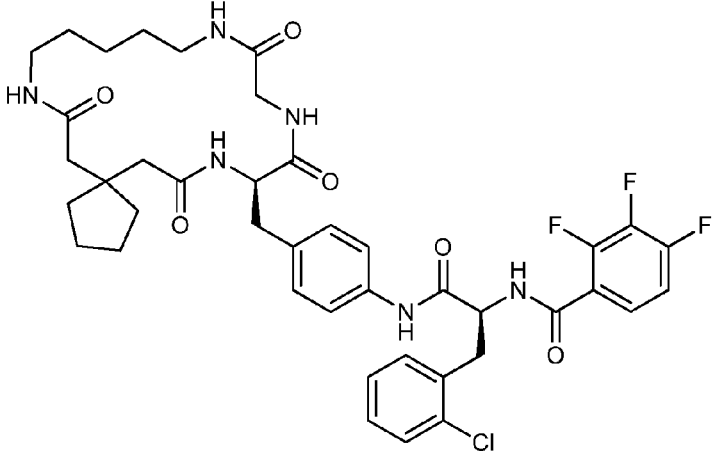
Compound No.	Structure
327	 <p>Chemical structure of Compound 327: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered amide ring) connected via a linker to a benzamide moiety. This benzamide is further connected to a pyridine ring via an amide linkage. The pyridine ring is substituted with a chlorine atom at the 2-position and a trifluoromethyl group at the 4-position.</p>
328	 <p>Chemical structure of Compound 328: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered amide ring) connected via a linker to a benzamide moiety. This benzamide is further connected to a pyridine ring via an amide linkage. The pyridine ring is substituted with a chlorine atom at the 2-position and a trifluoromethyl group at the 4-position.</p>

FIG. 12-103

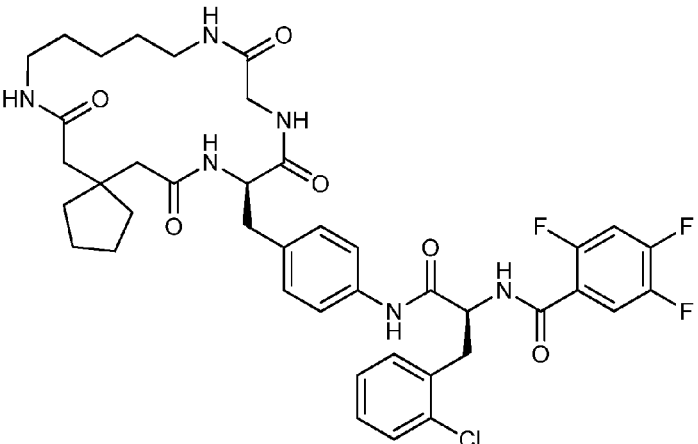
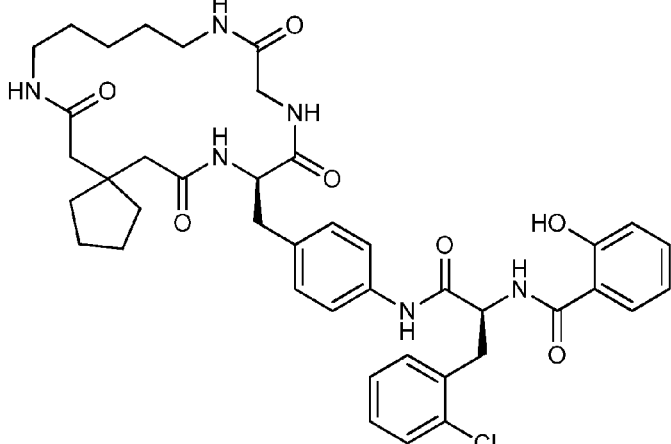
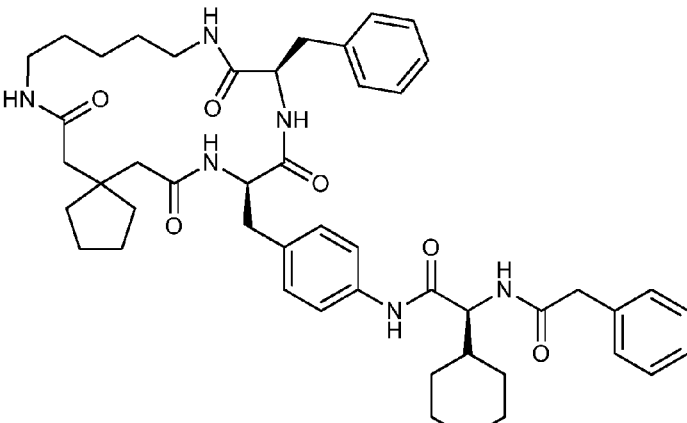
Compound No.	Structure
329	 <p>Chemical structure of Compound 329: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentane ring substituted with a long-chain amide group (HN-C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-) and a side chain containing a carbonyl group (C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-). The right side is a 2-chlorophenyl group linked via an amide bond to a 4-(2,4,6-trifluorophenyl)phenyl group, which is further linked via an amide bond to a 2-chlorophenyl group.</p>
330	 <p>Chemical structure of Compound 330: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentane ring substituted with a long-chain amide group (HN-C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-) and a side chain containing a carbonyl group (C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-). The right side is a 2-chlorophenyl group linked via an amide bond to a 4-(2-hydroxyphenyl)phenyl group, which is further linked via an amide bond to a 2-chlorophenyl group.</p>
331	 <p>Chemical structure of Compound 331: A complex molecule featuring a central amide linkage. The left side consists of a cyclopentane ring substituted with a long-chain amide group (HN-C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-) and a side chain containing a carbonyl group (C(=O)-CH2-CH2-CH2-CH2-CH2-CH2-NH-C(=O)-). The right side is a 2-chlorophenyl group linked via an amide bond to a 4-(2-phenylphenyl)phenyl group, which is further linked via an amide bond to a 2-chlorophenyl group.</p>

FIG. 12-104

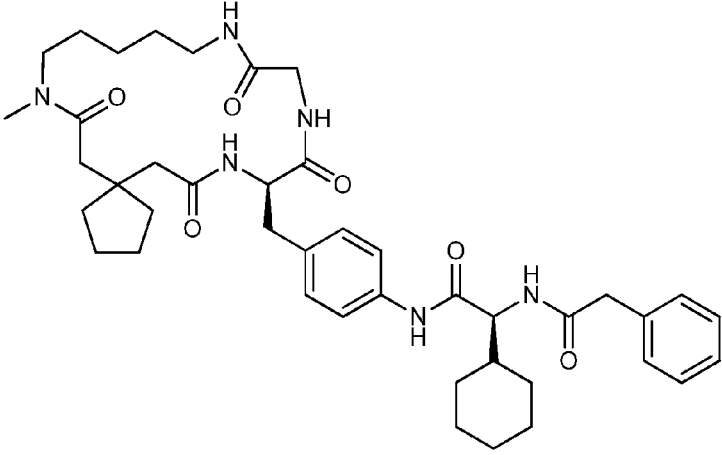
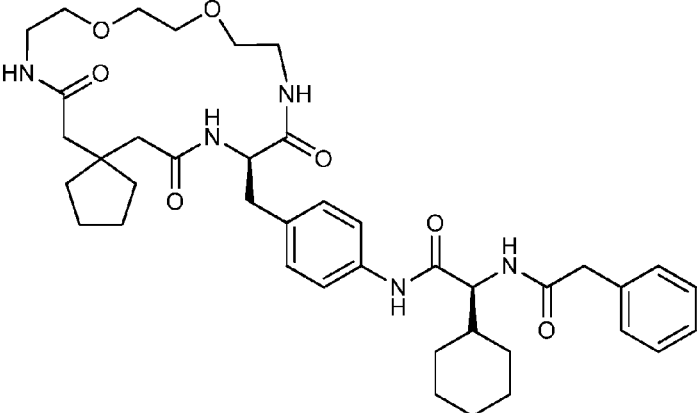
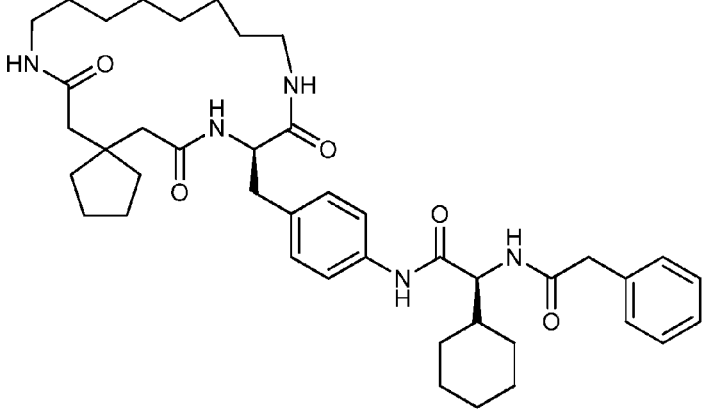
Compound No.	Structure
332	 <p>Chemical structure of Compound 332: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl group, and a phenyl group.</p>
333	 <p>Chemical structure of Compound 333: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl group, and a phenyl group.</p>
334	 <p>Chemical structure of Compound 334: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl group, and a phenyl group.</p>

FIG. 12-105

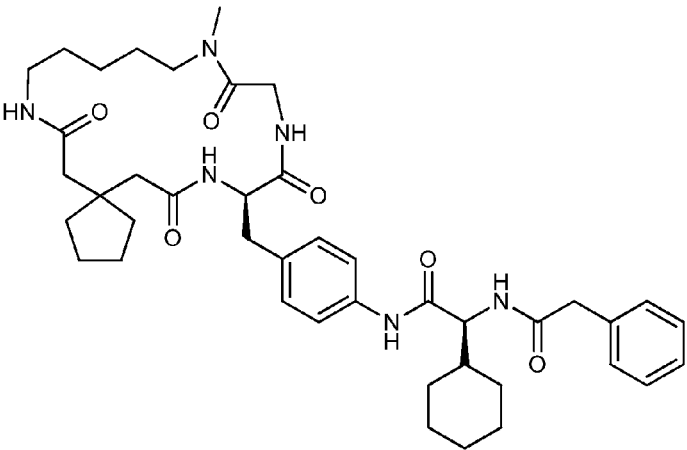
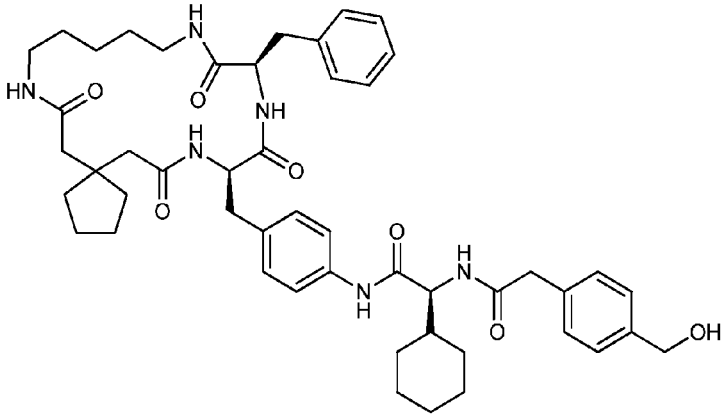
Compound No.	Structure
335	 <p>Chemical structure of Compound 335: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide and a carbonyl group). This system is linked via an amide bond to a chiral center (marked with a wedge bond) which is also part of a five-membered ring containing another amide and carbonyl group. This chiral center is further connected to a benzyl group, which is linked via an amide bond to another chiral center (marked with a wedge bond). This second chiral center is part of a five-membered ring with an amide and carbonyl group, and is also connected to a cyclohexyl group and a benzyl group. The benzyl group is linked via an amide bond to a third chiral center (marked with a wedge bond), which is part of a five-membered ring with an amide and carbonyl group, and is also connected to a benzyl group.</p>
336	 <p>Chemical structure of Compound 336: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide and a carbonyl group). This system is linked via an amide bond to a chiral center (marked with a wedge bond) which is also part of a five-membered ring containing another amide and carbonyl group. This chiral center is further connected to a benzyl group, which is linked via an amide bond to another chiral center (marked with a wedge bond). This second chiral center is part of a five-membered ring with an amide and carbonyl group, and is also connected to a cyclohexyl group and a benzyl group. The benzyl group is linked via an amide bond to a third chiral center (marked with a wedge bond), which is part of a five-membered ring with an amide and carbonyl group, and is also connected to a benzyl group. The benzyl group is linked via an amide bond to a third chiral center (marked with a wedge bond), which is part of a five-membered ring with an amide and carbonyl group, and is also connected to a benzyl group.</p>

FIG. 12-106

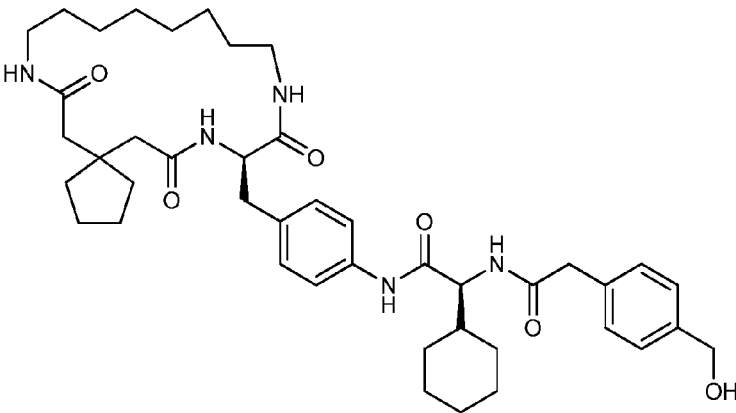
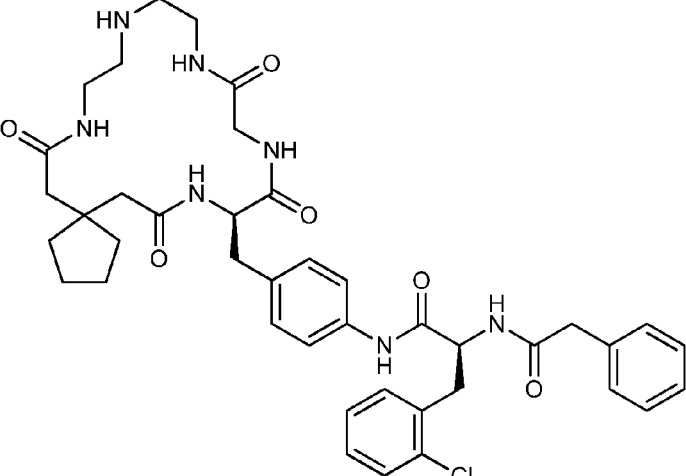
Compound No.	Structure
337	 <p>Chemical structure of Compound 337: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide. This amide is linked to a benzene ring, which is further connected to a cyclohexane ring via an amide bond. The cyclohexane ring is also substituted with a long-chain amide that terminates in a hydroxyl group.</p>
338	 <p>Chemical structure of Compound 338: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide. This amide is linked to a benzene ring, which is further connected to a cyclohexane ring via an amide bond. The cyclohexane ring is also substituted with a long-chain amide that terminates in a hydroxyl group.</p>

FIG. 12-107

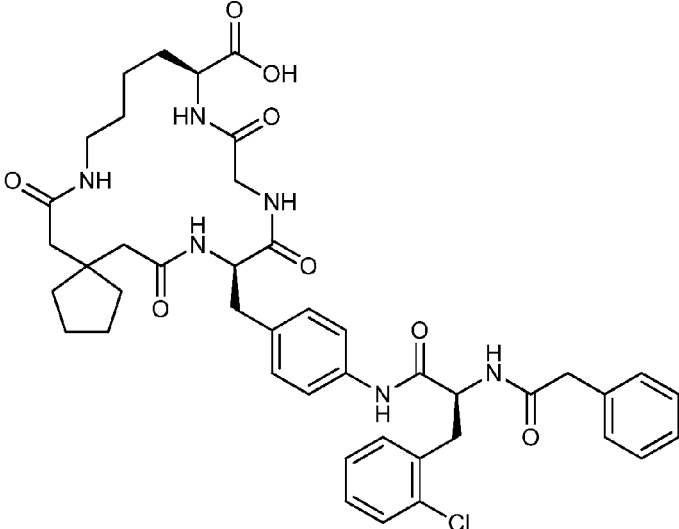
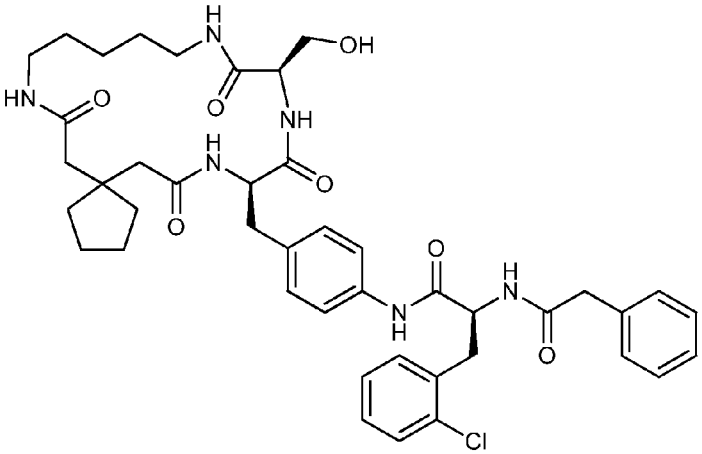
Compound No.	Structure
339	 <p>Chemical structure of Compound 339: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and a side chain containing multiple amide and ester linkages. The side chain includes a benzyl group, a 2-chlorophenyl group, and a 2-phenylacetamido group.</p>
340	 <p>Chemical structure of Compound 340: A complex molecule featuring a cyclopentane ring substituted with a hydroxyl group and a side chain containing multiple amide and ester linkages. The side chain includes a benzyl group, a 2-chlorophenyl group, and a 2-phenylacetamido group.</p>

FIG. 12-108

Compound No.	Structure
341	
342	

FIG. 12-109

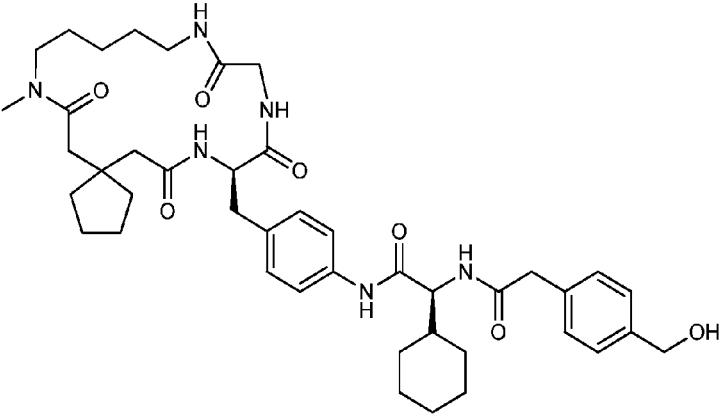
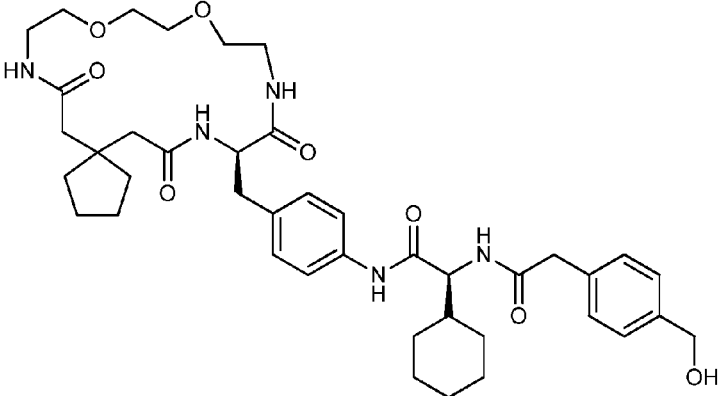
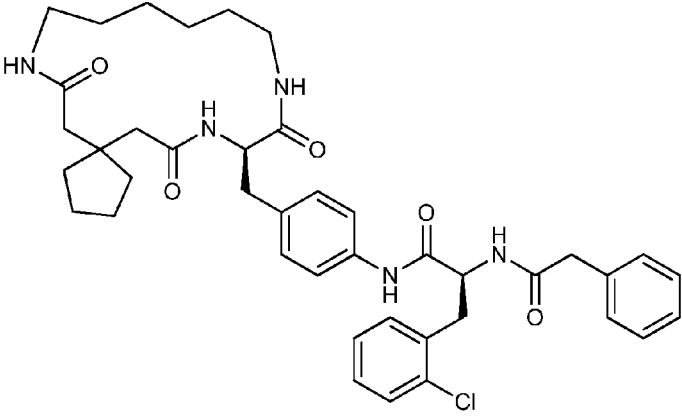
Compound No.	Structure
343	 <p>Chemical structure of Compound 343: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl ring, and a 4-hydroxybenzyl group.</p>
344	 <p>Chemical structure of Compound 344: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl ring, and a 4-hydroxybenzyl group.</p>
345	 <p>Chemical structure of Compound 345: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain is further substituted with a benzyl group, a cyclohexyl ring, and a 4-hydroxybenzyl group.</p>

FIG. 12-110

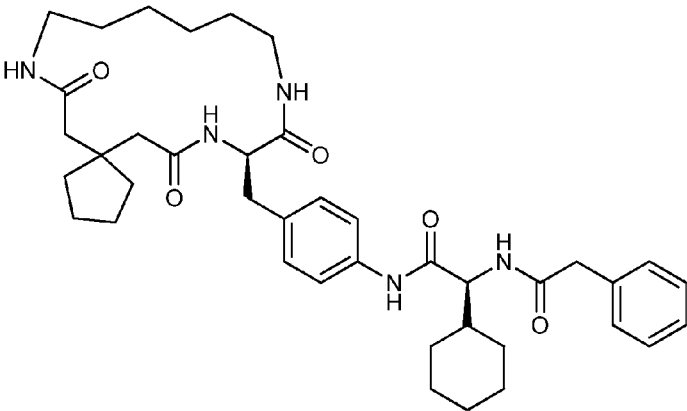
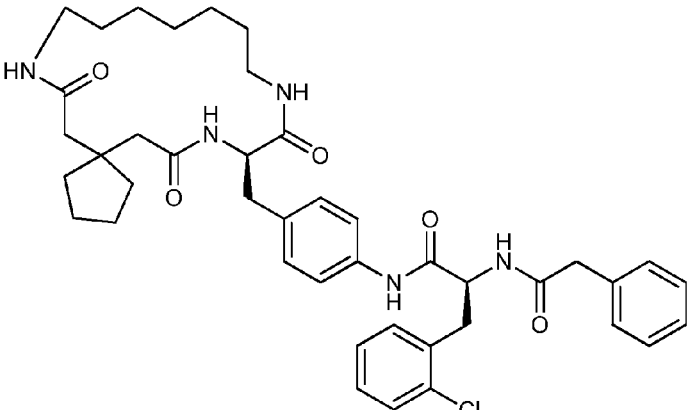
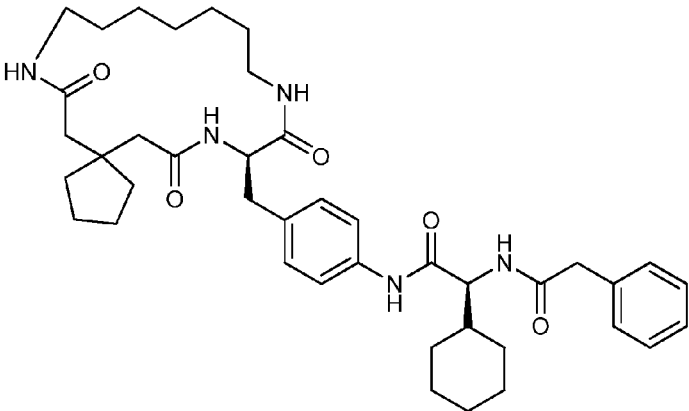
Compound No.	Structure
346	 <p>Chemical structure of Compound 346: A complex molecule featuring a long chain with multiple amide and carbamate groups. It includes a cyclopentyl ring, a benzene ring, and a cyclohexyl ring. The structure is highly branched and contains several functional groups.</p>
347	 <p>Chemical structure of Compound 347: A complex molecule featuring a long chain with multiple amide and carbamate groups. It includes a cyclopentyl ring, a benzene ring, and a cyclohexyl ring. The structure is highly branched and contains several functional groups.</p>
348	 <p>Chemical structure of Compound 348: A complex molecule featuring a long chain with multiple amide and carbamate groups. It includes a cyclopentyl ring, a benzene ring, and a cyclohexyl ring. The structure is highly branched and contains several functional groups.</p>

FIG. 12-111

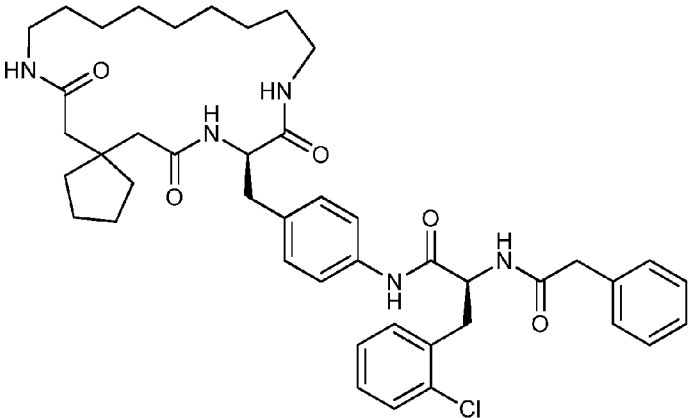
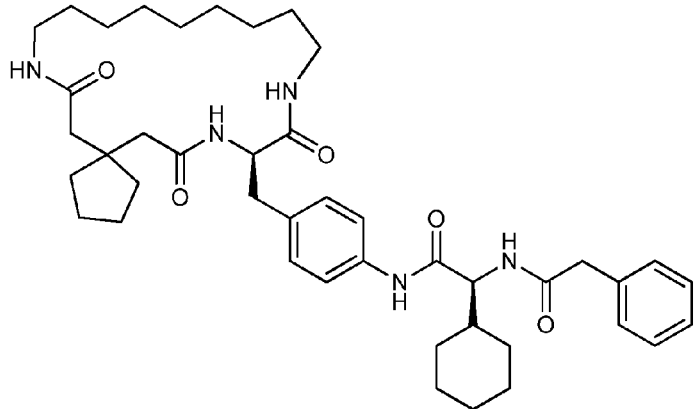
Compound No.	Structure
349	 <p>Chemical structure of Compound 349: A complex molecule featuring a long-chain amide (10-undecanamide) linked via an amide bond to a cyclopentylmethyl group. This cyclopentylmethyl group is further linked via an amide bond to a 4-((2-chlorophenyl)amino)-2-phenylpropanamide moiety. The 2-chlorophenyl group is substituted with a chlorine atom at the ortho position.</p>
350	 <p>Chemical structure of Compound 350: A complex molecule featuring a long-chain amide (10-undecanamide) linked via an amide bond to a cyclopentylmethyl group. This cyclopentylmethyl group is further linked via an amide bond to a 4-((cyclohexylamino)-2-phenylpropanamide moiety. The cyclohexyl group is substituted with a chlorine atom at the ortho position.</p>

FIG. 12-112

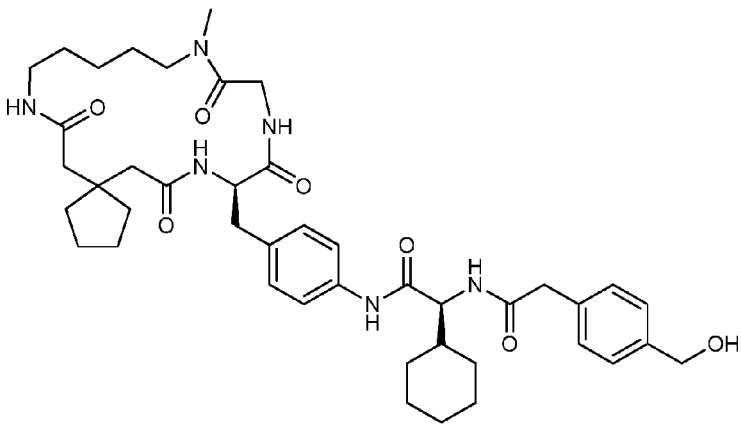
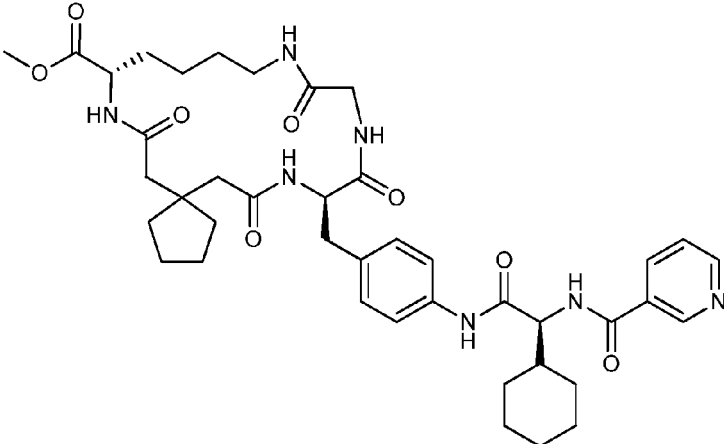
Compound No.	Structure
351	 <p>Chemical structure of Compound 351: A complex molecule featuring a central cyclohexane ring. The cyclohexane is substituted with a carboxamide group (-CONH-) and a carboxylic acid group (-COOH). The carboxamide group is further substituted with a long chain containing a cyclopentyl ring and a carboxamide group. The carboxylic acid group is further substituted with a long chain containing a cyclopentyl ring and a carboxamide group. The molecule also includes a benzamide group and a hydroxymethyl group.</p>
352	 <p>Chemical structure of Compound 352: A complex molecule featuring a central cyclohexane ring. The cyclohexane is substituted with a carboxamide group (-CONH-) and a carboxylic acid group (-COOH). The carboxamide group is further substituted with a long chain containing a cyclopentyl ring and a carboxamide group. The carboxylic acid group is further substituted with a long chain containing a cyclopentyl ring and a carboxamide group. The molecule also includes a benzamide group and a pyridine ring.</p>

FIG. 12-113

[illegible]

FIG. 12-114

Compound No.	Structure
356	
357	
358	

FIG. 12-115

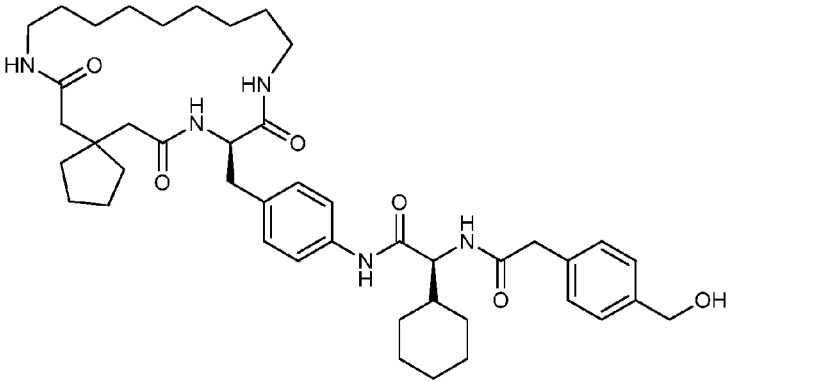
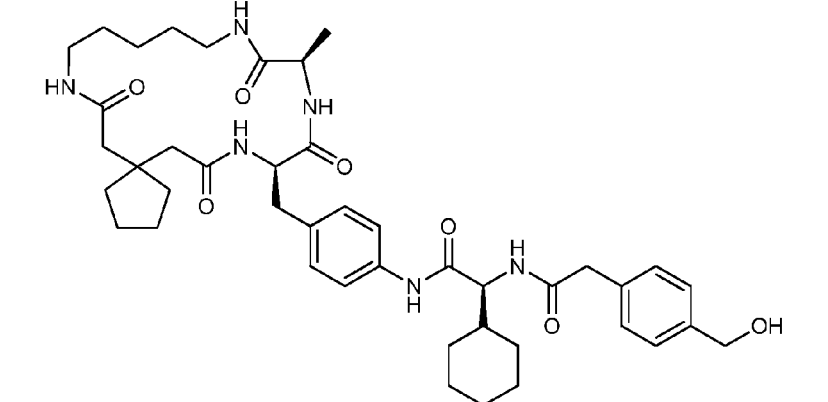
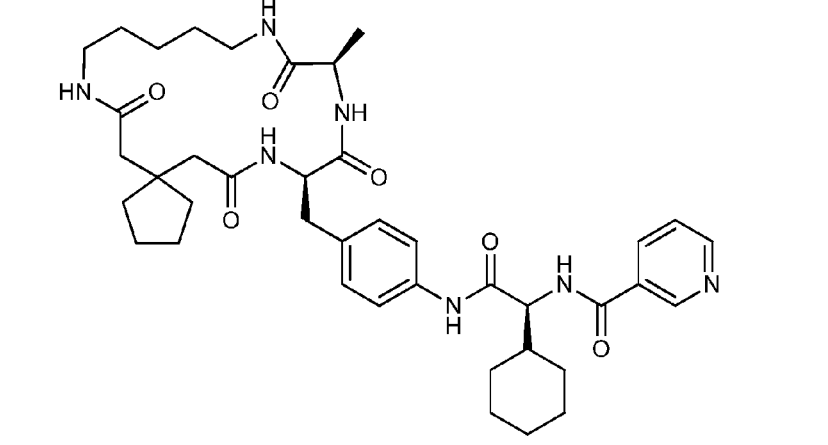
Compound No.	Structure
359	 <p>Chemical structure of Compound 359: A complex molecule featuring a cyclopentyl ring connected to a long-chain amide. This amide is linked to a benzene ring, which is further connected to a cyclohexyl ring. The structure also includes a hydroxymethyl group and a pyridine ring.</p>
360	 <p>Chemical structure of Compound 360: A complex molecule featuring a cyclopentyl ring connected to a long-chain amide. This amide is linked to a benzene ring, which is further connected to a cyclohexyl ring. The structure also includes a hydroxymethyl group and a pyridine ring.</p>
361	 <p>Chemical structure of Compound 361: A complex molecule featuring a cyclopentyl ring connected to a long-chain amide. This amide is linked to a benzene ring, which is further connected to a cyclohexyl ring. The structure also includes a hydroxymethyl group and a pyridine ring.</p>

FIG. 12-116

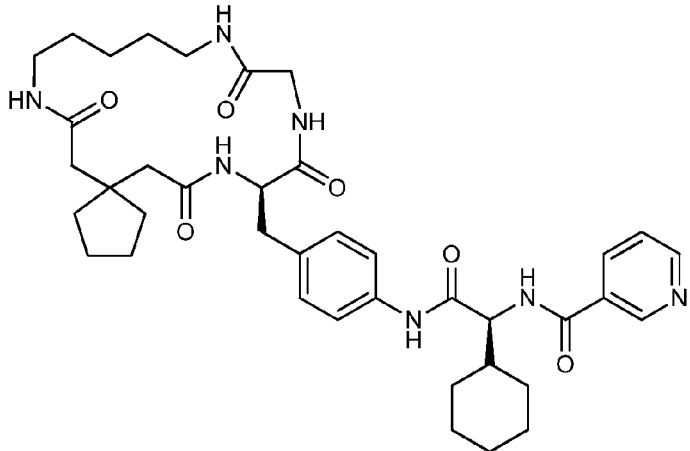
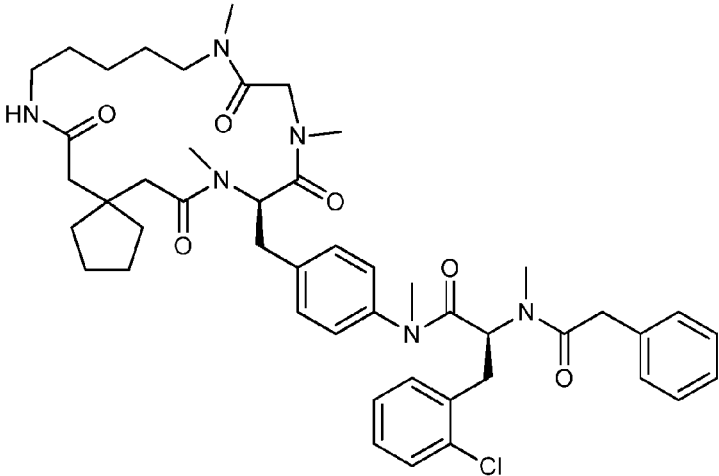
Compound No.	Structure
362	 <p>Chemical structure of Compound 362: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a methylene group to a benzene ring. The benzene ring is further connected to a chiral center (marked with a wedge bond) which is part of a chain containing two amide groups, a cyclohexane ring, and a pyridine ring.</p>
363	 <p>Chemical structure of Compound 363: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a methylene group to a benzene ring. The benzene ring is further connected to a chiral center (marked with a wedge bond) which is part of a chain containing two amide groups, a chlorophenyl ring, and a benzyl group.</p>

FIG. 12-117

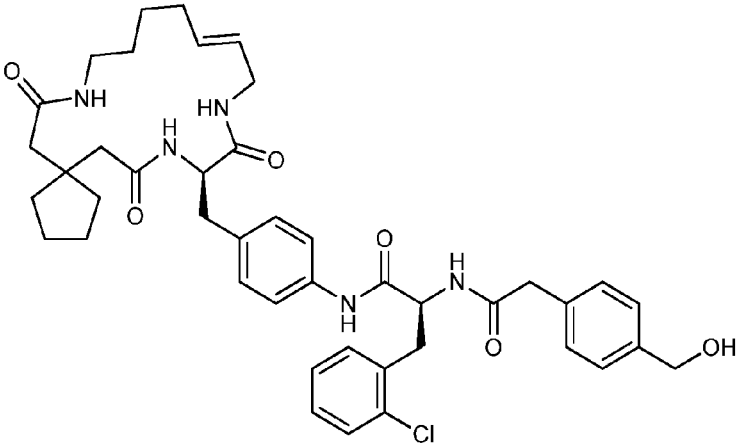
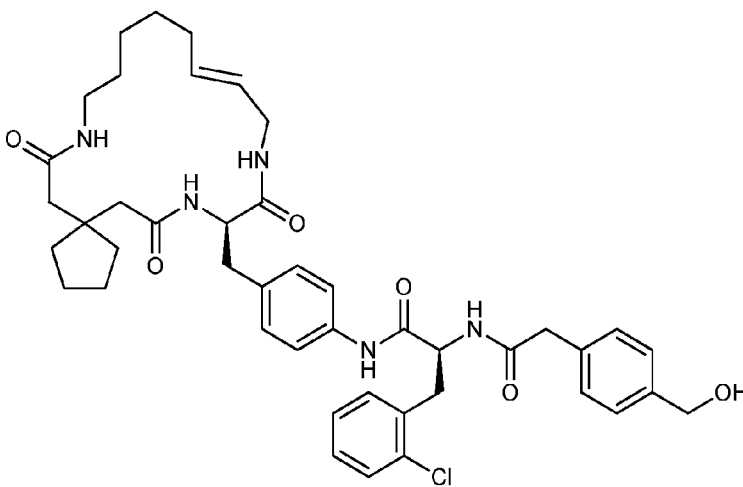
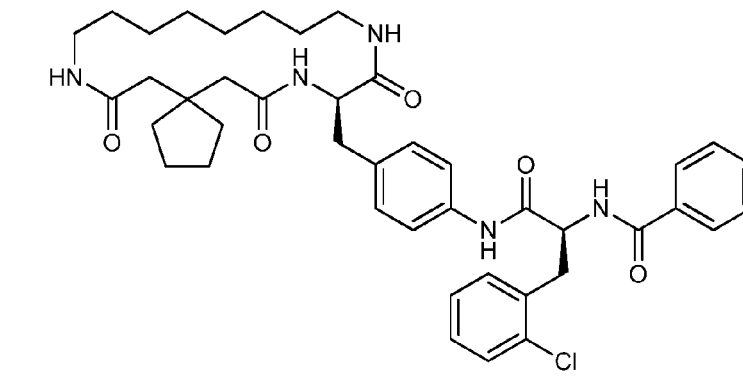
Compound No.	Structure
364	 <p>Chemical structure of compound 364. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups) connected via a chiral center to a benzyl group. This benzyl group is further connected to a chiral center that is part of a six-membered amide ring substituted with a 2-chlorophenyl group. This six-membered ring is also connected to a chiral center that is part of an amide linkage to a 4-hydroxybenzyl group.</p>
365	 <p>Chemical structure of compound 365. It is similar to compound 364, but the bicyclic amide system is replaced by a linear amide chain. The rest of the molecule, including the 2-chlorophenyl group and the 4-hydroxybenzyl group, remains the same.</p>
366	 <p>Chemical structure of compound 366. It features a bicyclic amide system similar to compound 364, but the amide linkage to the 4-hydroxybenzyl group is replaced by an amide linkage to a phenyl group. The rest of the molecule, including the 2-chlorophenyl group, remains the same.</p>

FIG. 12-118

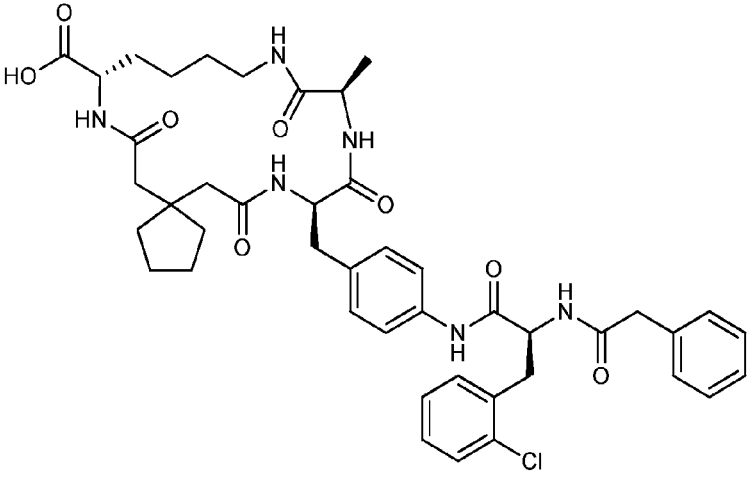
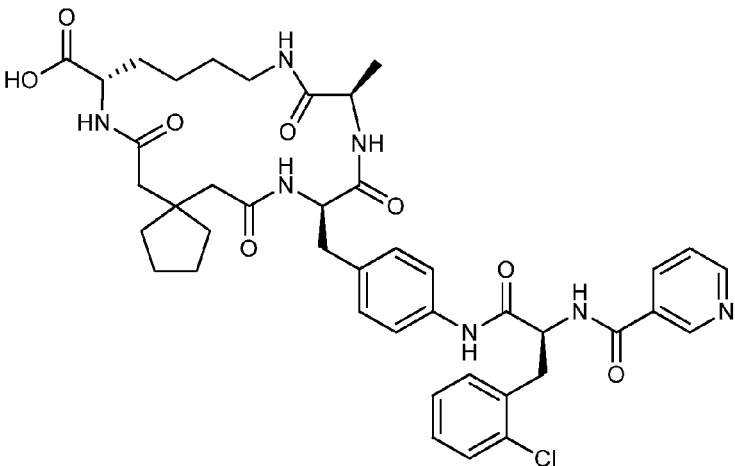
Compound No.	Structure
367	 <p>Chemical structure of Compound 367. It features a central cyclopentane ring substituted with a carboxylic acid group, a cyclopropylmethyl group, and a complex amide chain. The amide chain includes a 2-chlorophenyl group, a 3-chlorophenyl group, and a 4-phenyl group. Stereochemistry is indicated with wedges and dashes.</p>
368	 <p>Chemical structure of Compound 368. It is similar to Compound 367 but features a pyridine ring instead of a phenyl ring in the amide chain. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-119

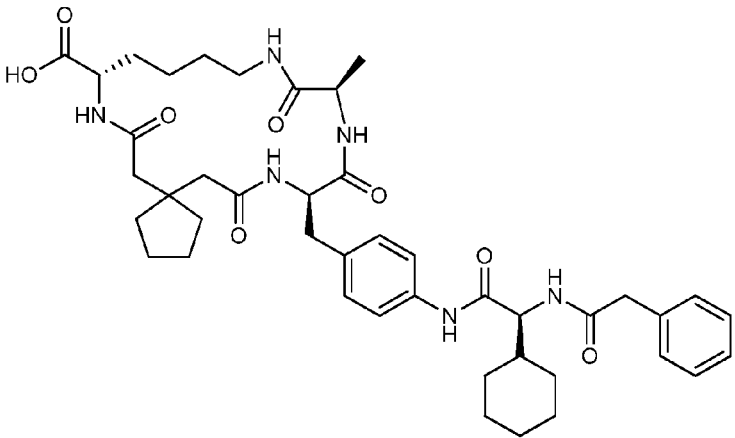
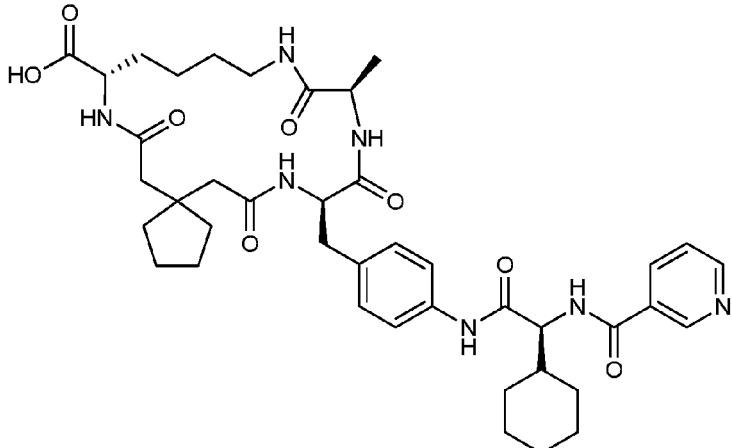
Compound No.	Structure
369	 <p>Chemical structure of Compound 369: A complex molecule featuring a central amide linkage. The left side includes a carboxylic acid group (HO-C=O) and a cyclopentyl ring. The right side includes a benzyl group, a benzamide group, and a cyclohexyl ring. Stereochemistry is indicated with wedges and dashes.</p>
370	 <p>Chemical structure of Compound 370: A complex molecule featuring a central amide linkage. The left side includes a carboxylic acid group (HO-C=O) and a cyclopentyl ring. The right side includes a benzyl group, a benzamide group, and a pyridine ring. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-120

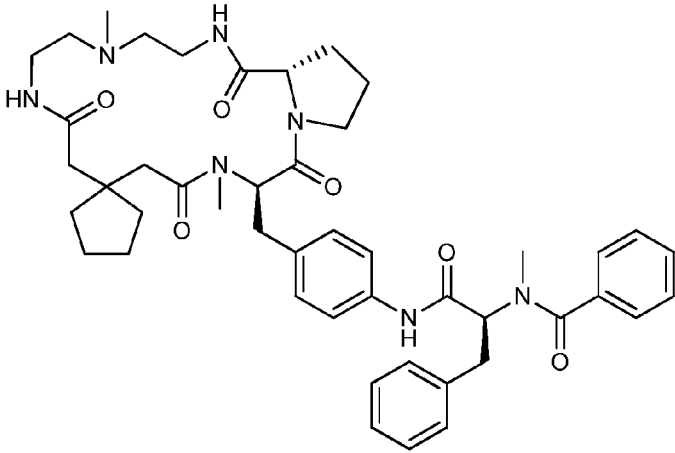
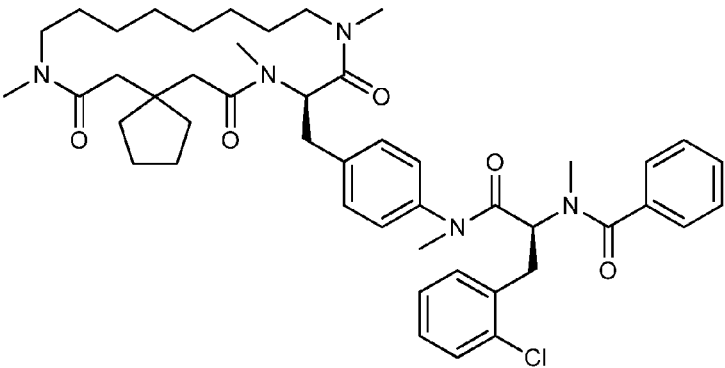
Compound No.	Structure
371	 <p>Chemical structure of Compound 371. It features a complex molecule with a central amide linkage. On the left, there is a cyclopentyl ring connected to a carbonyl group, which is part of a larger amide structure. This amide is linked to a chiral center (indicated by a wedge bond) that is also connected to a benzene ring. The benzene ring is further connected to another amide group, which is linked to a chiral center (indicated by a wedge bond) connected to a benzene ring. The molecule also includes a long, branched amide chain on the left side, featuring a cyclopentyl ring and a carbonyl group. The right side of the molecule includes a benzamide group and a carbonyl group.</p>
372	 <p>Chemical structure of Compound 372. It is similar to Compound 371, but with a different amide chain on the left side. The left side features a long, branched amide chain with a cyclopentyl ring and a carbonyl group. The central part of the molecule is identical to Compound 371, featuring a chiral center connected to a benzene ring, which is further connected to another amide group and a chiral center connected to a benzene ring. The right side of the molecule includes a benzamide group and a carbonyl group.</p>

FIG. 12-121

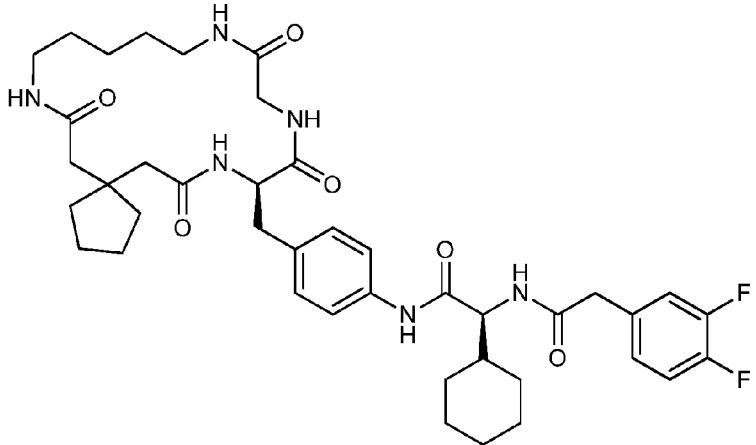
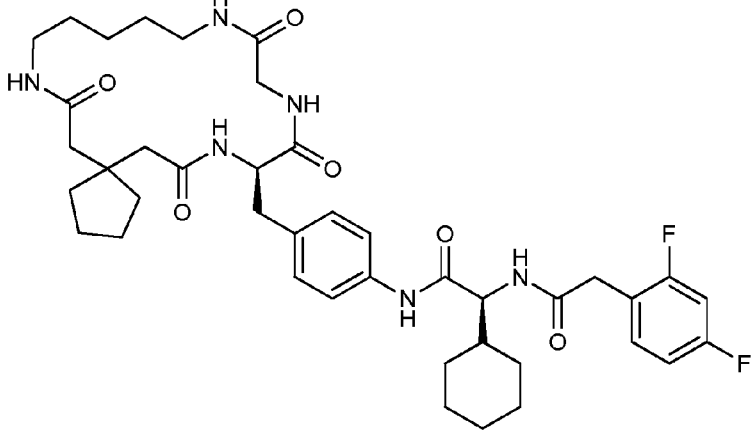
Compound No.	Structure
373	 <p>Chemical structure of Compound 373: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center (indicated by a wedge bond) to a benzene ring. The benzene ring is further substituted with an amide group, which is connected to a cyclohexane ring. The cyclohexane ring is also linked via a chiral center (indicated by a wedge bond) to another amide group, which is connected to a 2,4-difluorophenyl group.</p>
374	 <p>Chemical structure of Compound 374: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center (indicated by a wedge bond) to a benzene ring. The benzene ring is further substituted with an amide group, which is connected to a cyclohexane ring. The cyclohexane ring is also linked via a chiral center (indicated by a wedge bond) to another amide group, which is connected to a 2,4-difluorophenyl group.</p>

FIG. 12-122

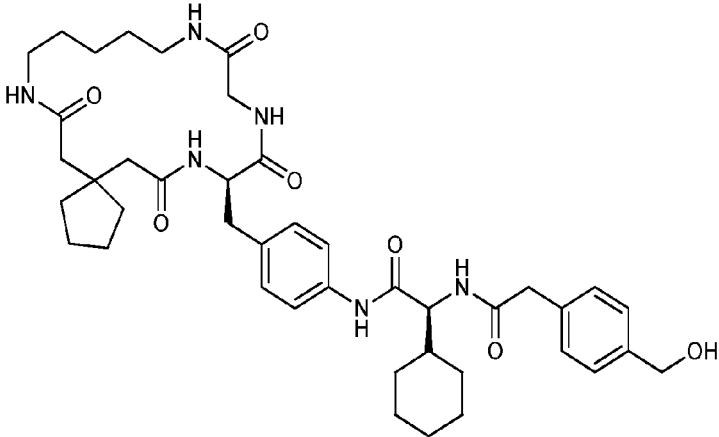
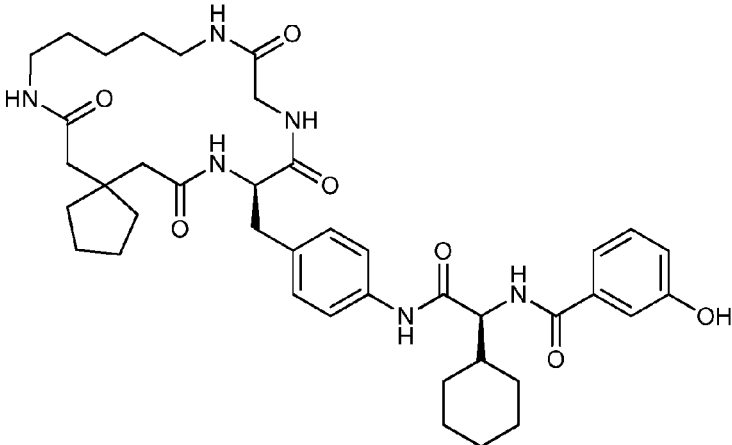
Compound No.	Structure
375	 <p>Chemical structure of Compound 375: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a cyclohexyl group and a side chain ending in a hydroxymethyl group.</p>
376	 <p>Chemical structure of Compound 376: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a cyclohexyl group and a side chain ending in a phenol group.</p>

FIG. 12-123

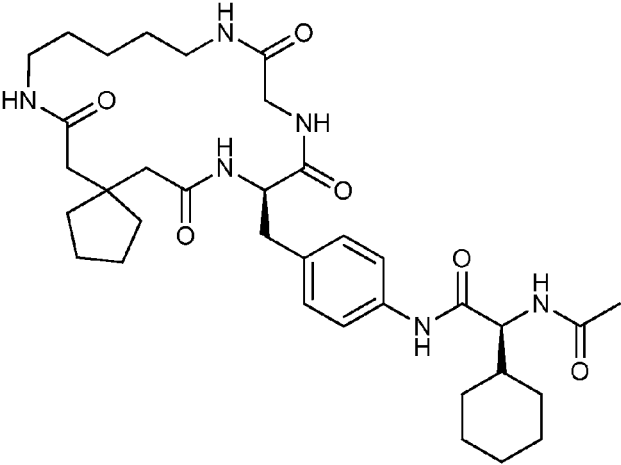
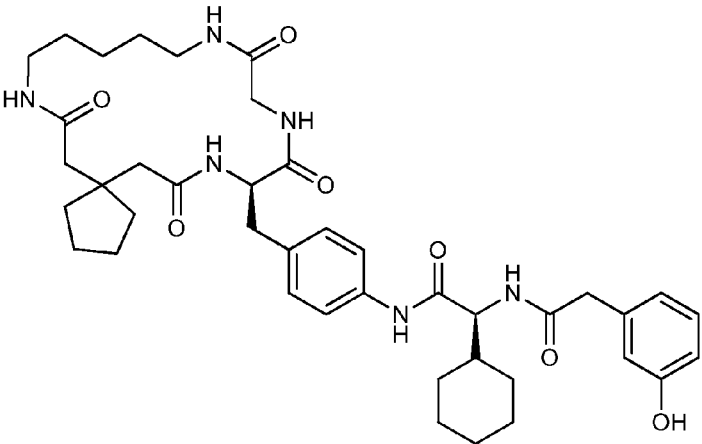
Compound No.	Structure
377	 <p>Chemical structure of Compound 377: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzene ring, which is further connected to a side chain containing a cyclohexyl group and an amide linkage to a 4-hydroxyphenyl group.</p>
378	 <p>Chemical structure of Compound 378: Similar to Compound 377, it features the same bicyclic amide core. However, the side chain is modified, featuring a cyclohexyl group and an amide linkage to a 4-hydroxyphenyl group, with a different overall connectivity compared to Compound 377.</p>

FIG. 12-124

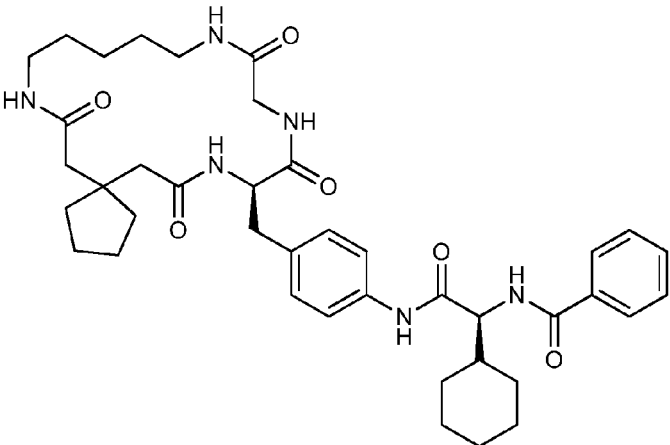
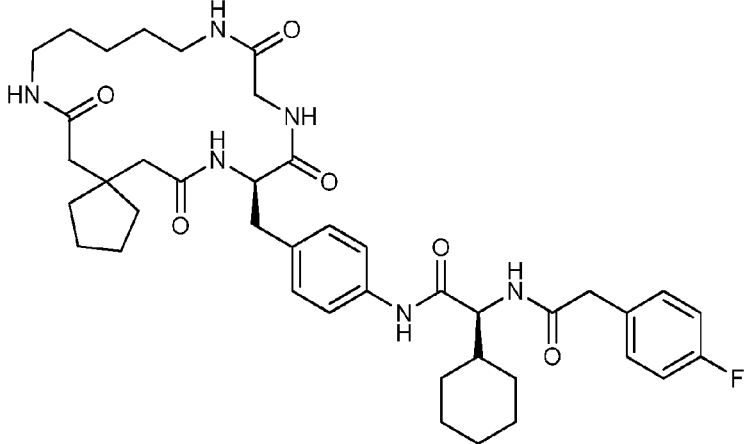
Compound No.	Structure
379	 <p>Chemical structure of Compound 379: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a cyclohexane ring) connected via an amide linkage to a chain containing a benzamide moiety, a cyclohexyl group, and a benzoyl group.</p>
380	 <p>Chemical structure of Compound 380: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a cyclohexane ring) connected via an amide linkage to a chain containing a benzamide moiety, a cyclohexyl group, and a 4-fluorophenyl group.</p>

FIG. 12-125

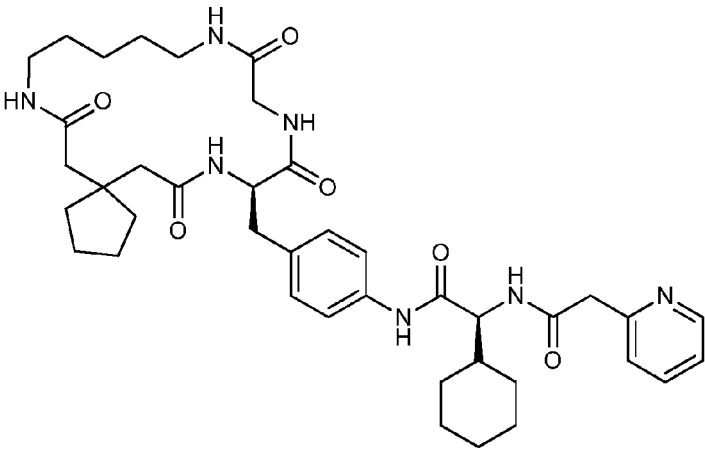
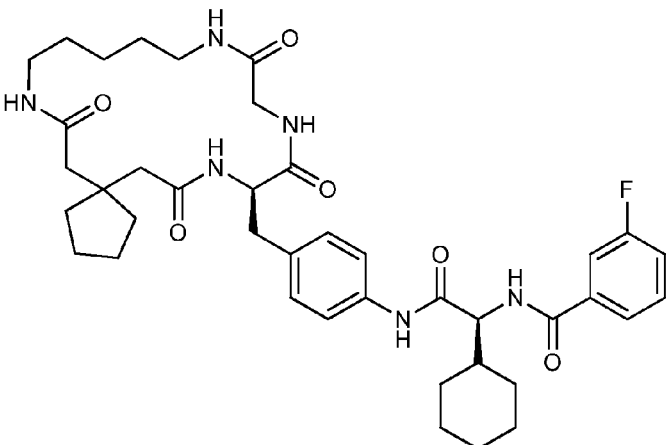
Compound No.	Structure
381	 <p>Chemical structure of Compound 381: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a cyclohexane ring) connected via an amide linkage to a benzene ring. The benzene ring is further substituted with an amide group, which is linked to a cyclohexane ring. The cyclohexane ring is also substituted with an amide group, which is linked to a pyridine ring.</p>
382	 <p>Chemical structure of Compound 382: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a cyclohexane ring) connected via an amide linkage to a benzene ring. The benzene ring is further substituted with an amide group, which is linked to a cyclohexane ring. The cyclohexane ring is also substituted with an amide group, which is linked to a 4-fluorophenyl ring.</p>

FIG. 12-126

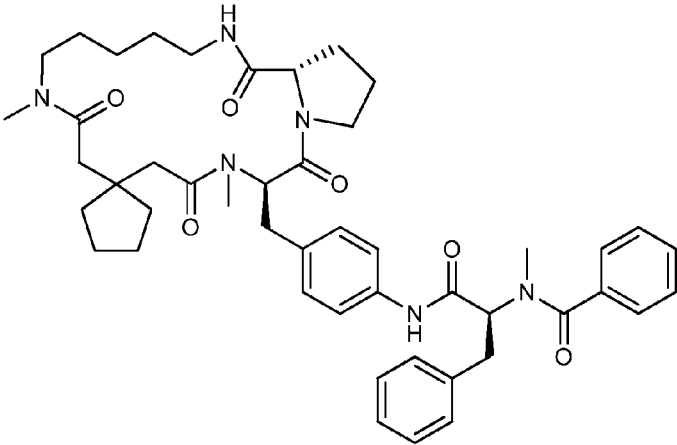
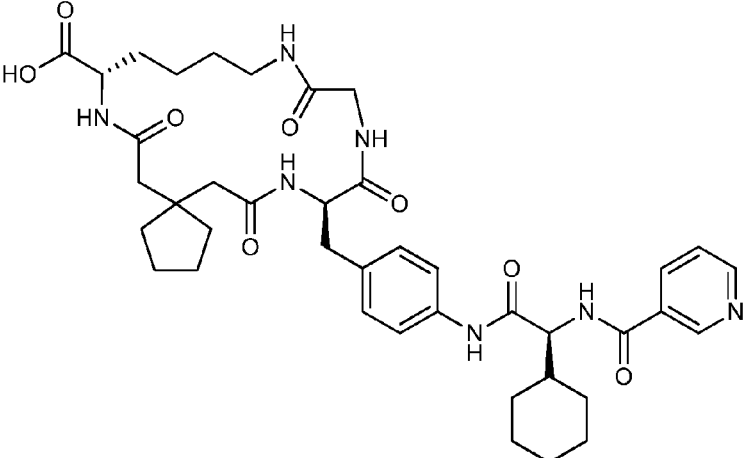
Compound No.	Structure
383	 <p>Chemical structure of Compound 383: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a nitrogen atom. The right side includes a benzamide moiety connected to a carbonyl group, which is further linked to a nitrogen atom. The structure also contains a cyclopentyl ring and a benzamide moiety.</p>
384	 <p>Chemical structure of Compound 384: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a nitrogen atom. The right side includes a benzamide moiety connected to a carbonyl group, which is further linked to a nitrogen atom. The structure also contains a cyclopentyl ring and a benzamide moiety.</p>

FIG. 12-127

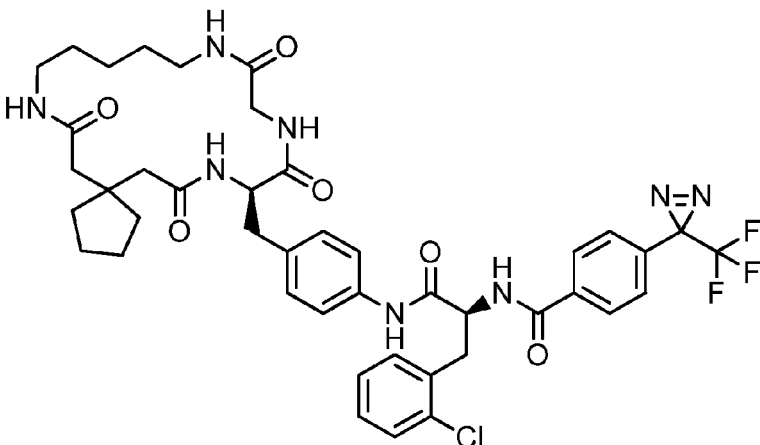
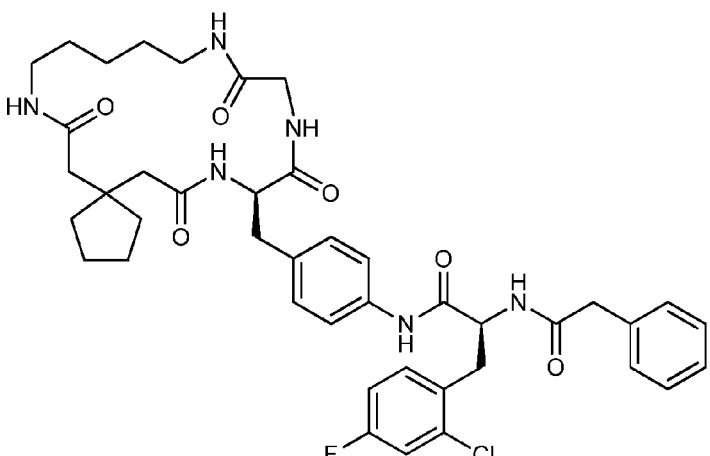
Compound No.	Structure
385	 <p>Chemical structure of Compound 385: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and carbamate groups. The chain includes a 4-chlorophenyl ring, a 2-chlorophenyl ring, and a 4-(trifluoromethyl)phenyl ring. The structure is highly branched and contains multiple amide and carbamate linkages.</p>
386	 <p>Chemical structure of Compound 386: A complex molecule featuring a cyclopentyl ring connected to a chain of amide and carbamate groups. The chain includes a 4-chlorophenyl ring, a 2-chlorophenyl ring, and a 4-(trifluoromethyl)phenyl ring. The structure is highly branched and contains multiple amide and carbamate linkages.</p>

FIG. 12-128

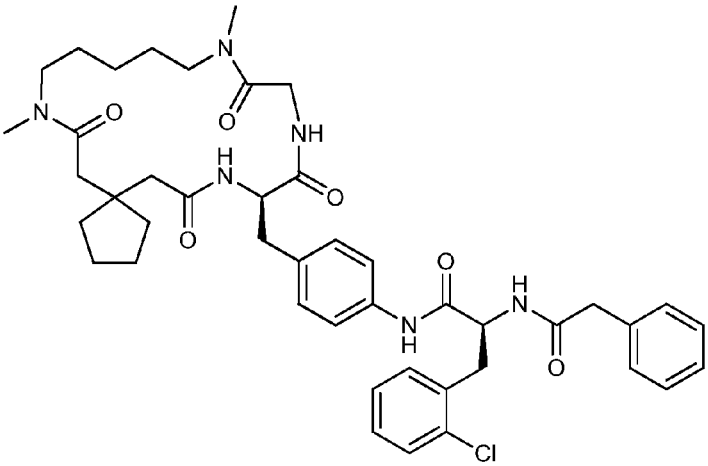
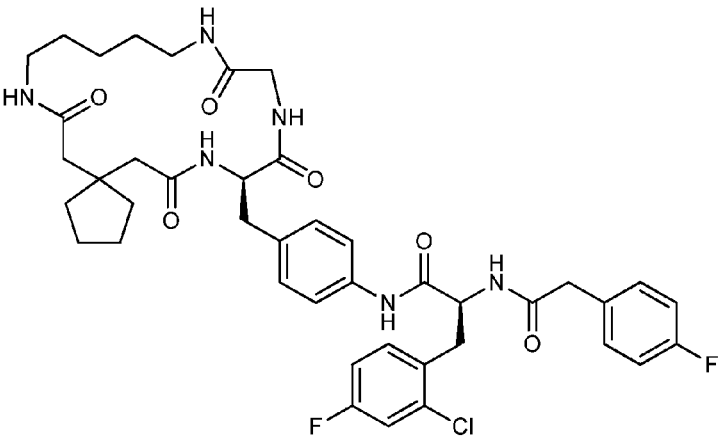
Compound No.	Structure
387	 <p>Chemical structure of Compound 387. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a carbonyl group and a dimethylamino group). This is linked via an amide bond to a chiral center, which is further connected to a benzyl group. The benzyl group is linked to another chiral center, which is connected to a benzyl group with a chlorine substituent. The final part of the molecule is a benzyl group with a fluorine substituent.</p>
388	 <p>Chemical structure of Compound 388. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a carbonyl group and a dimethylamino group). This is linked via an amide bond to a chiral center, which is further connected to a benzyl group. The benzyl group is linked to another chiral center, which is connected to a benzyl group with a chlorine substituent. The final part of the molecule is a benzyl group with a fluorine substituent.</p>

FIG. 12-129

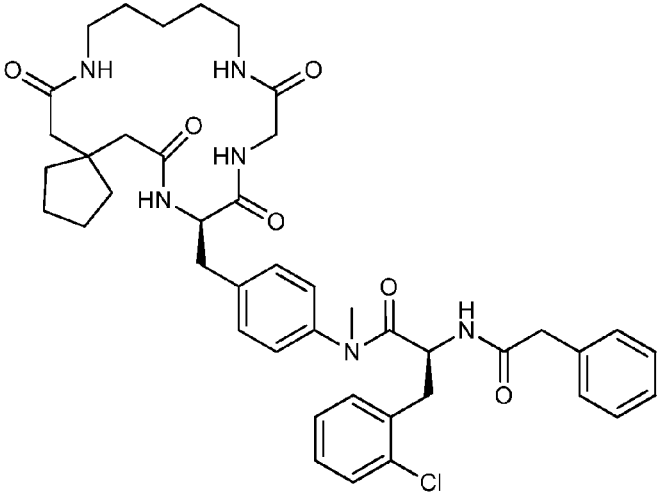
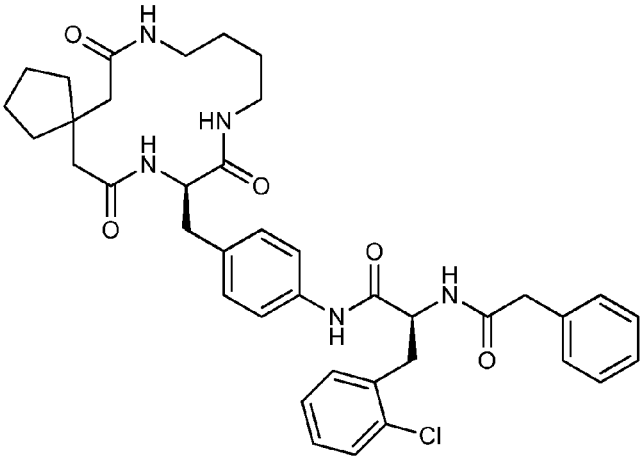
Compound No.	Structure
390	 <p>Chemical structure of Compound 390: A complex molecule featuring a cyclopentane ring substituted with a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group and a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The cyclopentane ring is also substituted with a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The molecule includes a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group, a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group, and a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The molecule is a complex amide derivative.</p>
391	 <p>Chemical structure of Compound 391: A complex molecule featuring a cyclopentane ring substituted with a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group and a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The cyclopentane ring is also substituted with a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The molecule includes a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group, a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group, and a 1,4-bis(hexamethyleneamino)butane-1,4-dicarboxamide group. The molecule is a complex amide derivative.</p>

FIG. 12-130

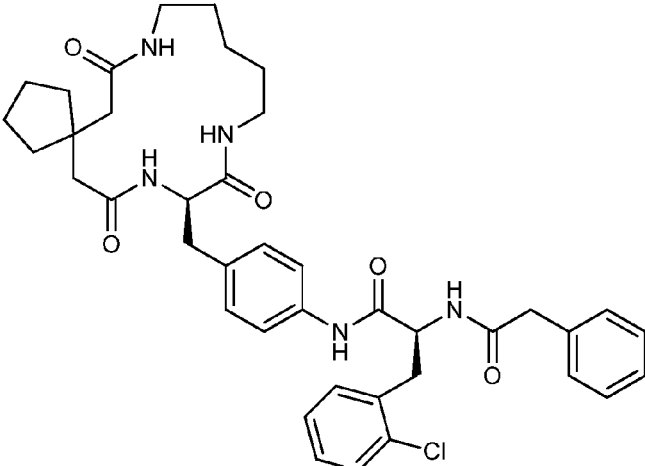
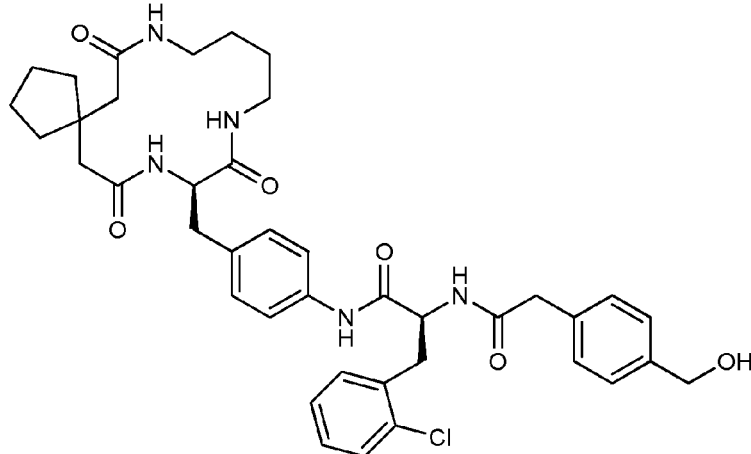
Compound No.	Structure
392	 <p>Chemical structure of Compound 392: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH) and a carboxylic acid group (COOH). The carboxamide group is linked via a methylene chain to a chiral center (C*) which is also bonded to a carboxylic acid group (COOH) and a benzyl group (CH2-Ph). The benzyl group is further linked via a methylene chain to another chiral center (C*) which is bonded to a carboxylic acid group (COOH) and a 2-chlorophenyl group (2-Cl-Ph). The 2-chlorophenyl group is linked via a methylene chain to a third chiral center (C*) which is bonded to a carboxylic acid group (COOH) and a benzyl group (CH2-Ph).</p>
393	 <p>Chemical structure of Compound 393: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH) and a carboxylic acid group (COOH). The carboxamide group is linked via a methylene chain to a chiral center (C*) which is also bonded to a carboxylic acid group (COOH) and a benzyl group (CH2-Ph). The benzyl group is further linked via a methylene chain to another chiral center (C*) which is bonded to a carboxylic acid group (COOH) and a 2-chlorophenyl group (2-Cl-Ph). The 2-chlorophenyl group is linked via a methylene chain to a third chiral center (C*) which is bonded to a carboxylic acid group (COOH) and a benzyl group (CH2-Ph). The benzyl group is further linked via a methylene chain to a fourth chiral center (C*) which is bonded to a carboxylic acid group (COOH) and a benzyl group (CH2-Ph).</p>

FIG. 12-131

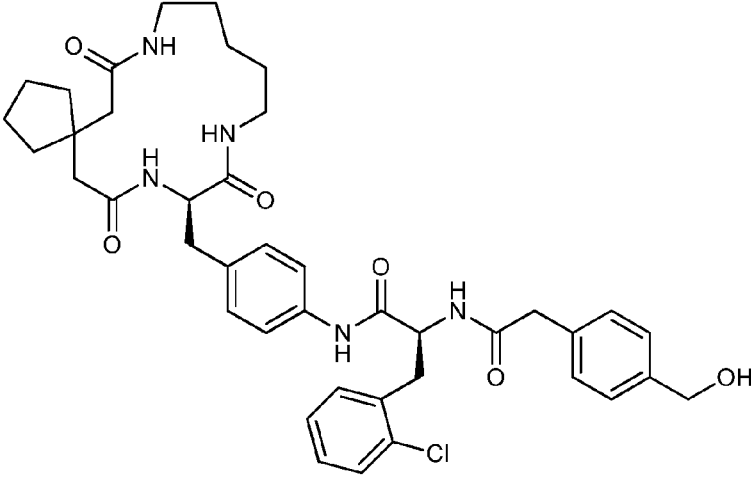
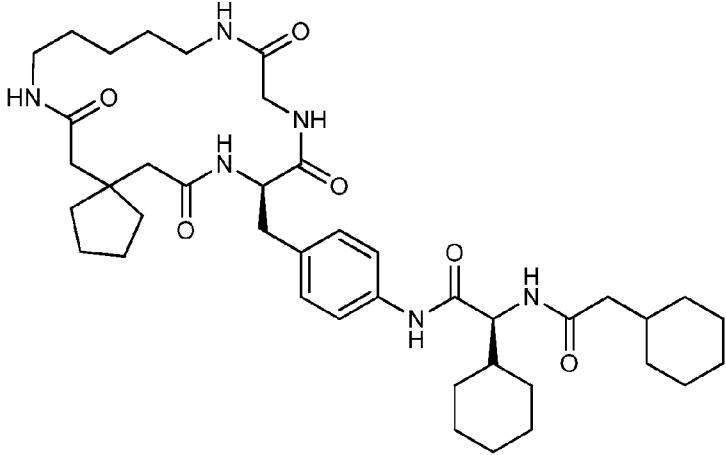
Compound No.	Structure
394	 <p>Chemical structure of Compound 394: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C=O) and a carboxylic acid derivative (NH-C(=O)-CH2-). This is linked via an amide bond to a benzene ring, which is further connected to a chiral center (C*) bonded to a carboxamide group (NH-C(=O)-CH2-). This chiral center is also linked to another benzene ring, which is connected to a carboxylic acid derivative (NH-C(=O)-CH2-). The molecule also includes a 2-chlorophenyl group and a 4-hydroxybenzyl group.</p>
395	 <p>Chemical structure of Compound 395: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C=O) and a carboxylic acid derivative (NH-C(=O)-CH2-). This is linked via an amide bond to a benzene ring, which is further connected to a chiral center (C*) bonded to a carboxamide group (NH-C(=O)-CH2-). This chiral center is also linked to another benzene ring, which is connected to a carboxylic acid derivative (NH-C(=O)-CH2-). The molecule also includes a cyclohexyl group and a 4-cyclohexylmethyl group.</p>

FIG. 12-132

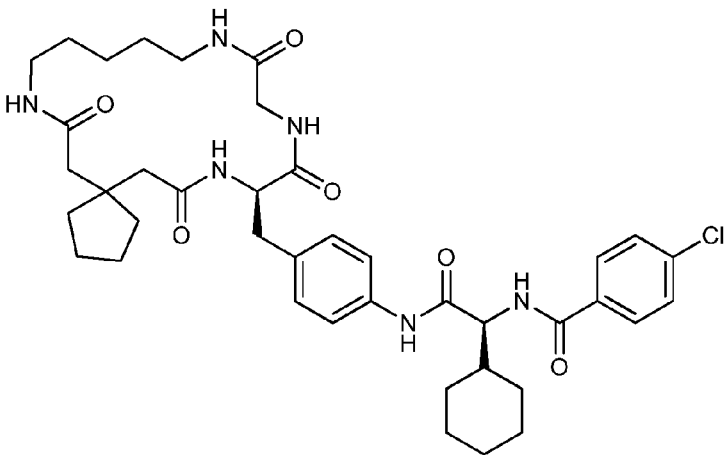
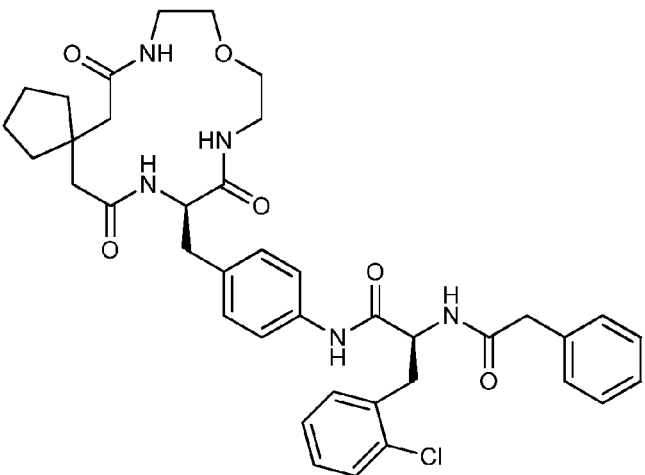
Compound No.	Structure
396	 <p>Chemical structure of Compound 396: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is part of a larger amide chain. The right side features a benzene ring connected to a carbonyl group, which is further linked to a cyclohexyl ring and a 4-chlorophenyl group.</p>
397	 <p>Chemical structure of Compound 397: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is part of a larger amide chain. The right side features a benzene ring connected to a carbonyl group, which is further linked to a 2-chlorophenyl group and a benzyl group.</p>

FIG. 12-133

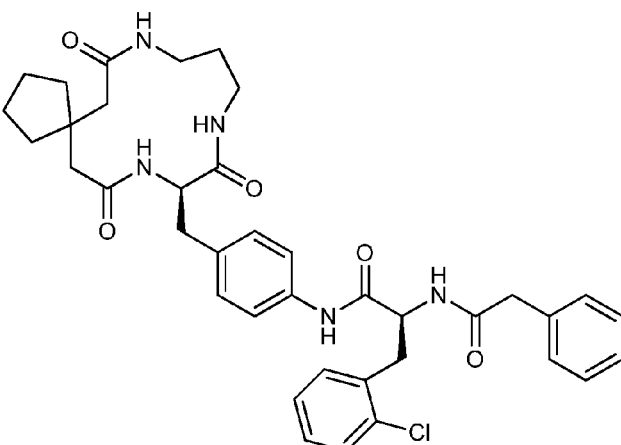
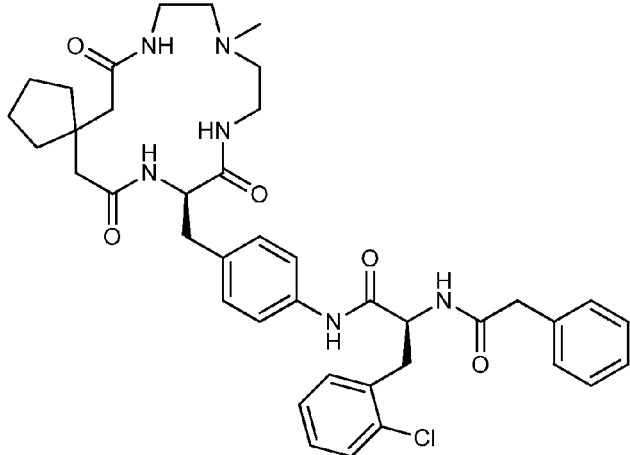
Compound No.	Structure
398	 <p>Chemical structure of compound 398. It features a cyclopentane ring substituted with a 1,3-bis(carbamoyl)propan-2-yl group. One carbamoyl group is attached to a 1,3-bis(carbamoyl)propan-2-yl chain, which is further substituted with a 4-(2-chlorophenyl)phenyl group and a 2-phenylacetamido group. The other carbamoyl group is attached to a 2-chlorophenyl group.</p>
399	 <p>Chemical structure of compound 399. It is similar to compound 398, but the 1,3-bis(carbamoyl)propan-2-yl group is replaced by a 1,3-bis(carbamoyl)propan-2-yl group where the nitrogen atom is substituted with a methyl group.</p>

FIG. 12-134

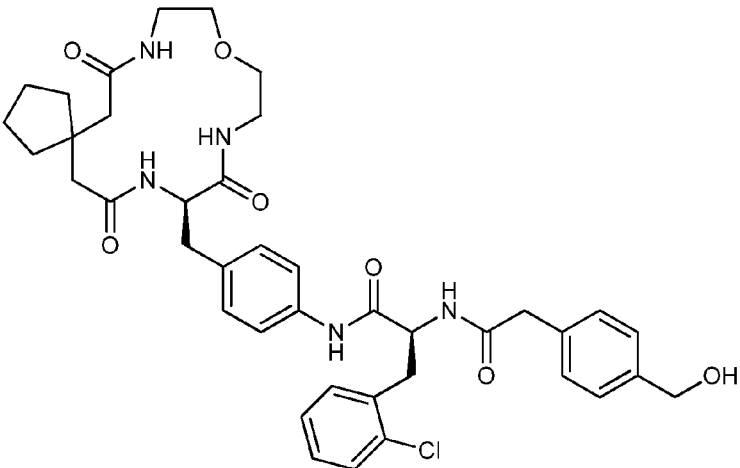
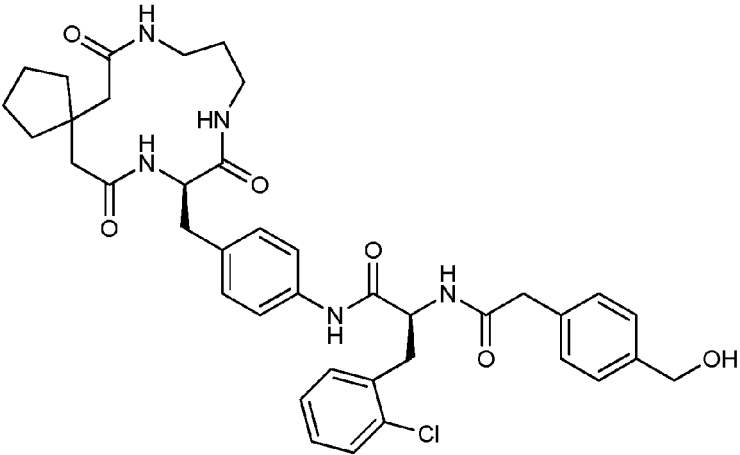
Compound No.	Structure
400	 <p>Chemical structure of compound 400. It features a cyclopentane ring substituted with a 1,3-dioxolane ring and a 1,3-dioxane ring, both connected via amide linkages. The 1,3-dioxane ring is further substituted with a 4-(2-(4-hydroxybenzyl)carbamoyl)-2-(2-chlorophenyl)phenyl group.</p>
401	 <p>Chemical structure of compound 401. It features a cyclopentane ring substituted with a 1,3-dioxolane ring and a 1,3-dioxane ring, both connected via amide linkages. The 1,3-dioxane ring is further substituted with a 4-(2-(4-hydroxybenzyl)carbamoyl)-2-(2-chlorophenyl)phenyl group.</p>

FIG. 12-135

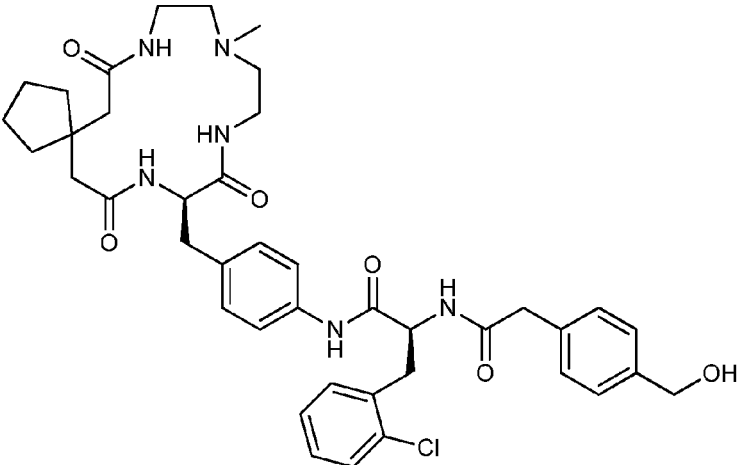
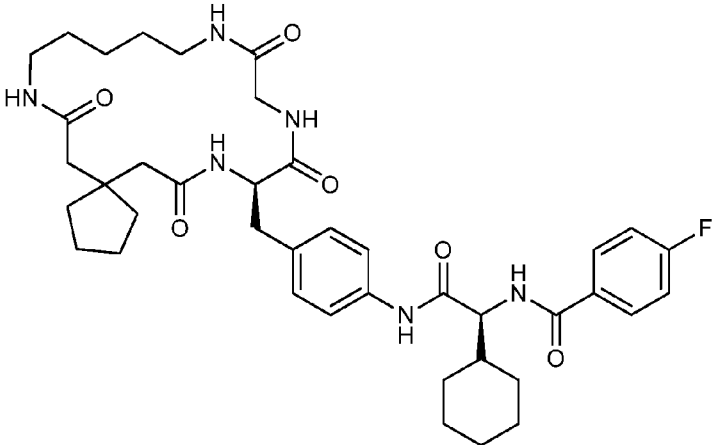
Compound No.	Structure
402	 <p>Chemical structure of Compound 402: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group, which is part of a larger amide chain. The chain includes a benzyl group, a 2-chlorophenyl group, and a 4-hydroxybenzyl group.</p>
403	 <p>Chemical structure of Compound 403: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group, which is part of a larger amide chain. The chain includes a benzyl group, a cyclohexyl group, and a 4-fluorophenyl group.</p>

FIG. 12-136

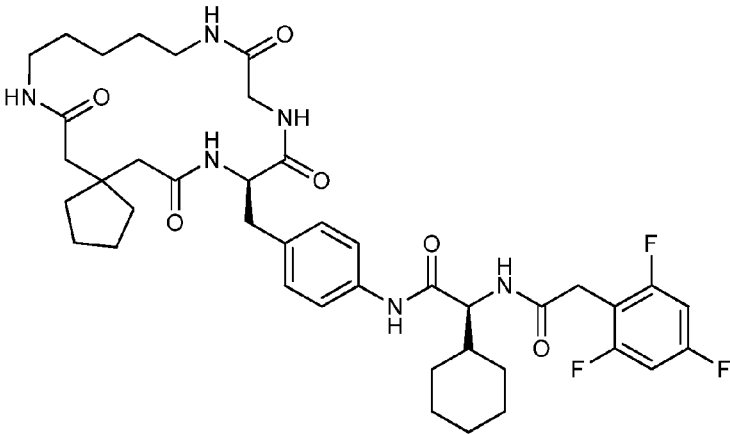
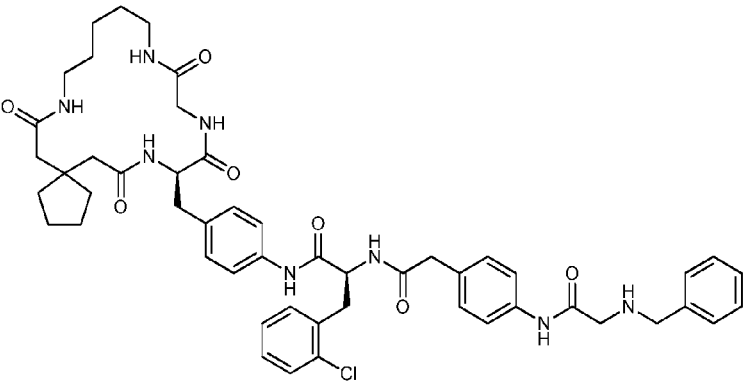
Compound No.	Structure
404	 <p>Chemical structure of Compound 404: A complex molecule featuring a cyclopentane ring substituted with a 6-oxo-1,6,7,8-tetrahydro-2H-pyrimidin-2-yl group and a 2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl group. The benzothiazole ring is further substituted with a 4-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group. The benzothiazole ring is also substituted with a 2-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group. The benzothiazole ring is also substituted with a 2-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group.</p>
405	 <p>Chemical structure of Compound 405: A complex molecule featuring a cyclopentane ring substituted with a 6-oxo-1,6,7,8-tetrahydro-2H-pyrimidin-2-yl group and a 2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl group. The benzothiazole ring is further substituted with a 4-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group. The benzothiazole ring is also substituted with a 2-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group. The benzothiazole ring is also substituted with a 2-((2-((2-oxo-1,2,3,4-tetrahydro-5H-benzothiazol-5-yl)amino)propanamido)phenyl)propanamido group.</p>

FIG. 12-137

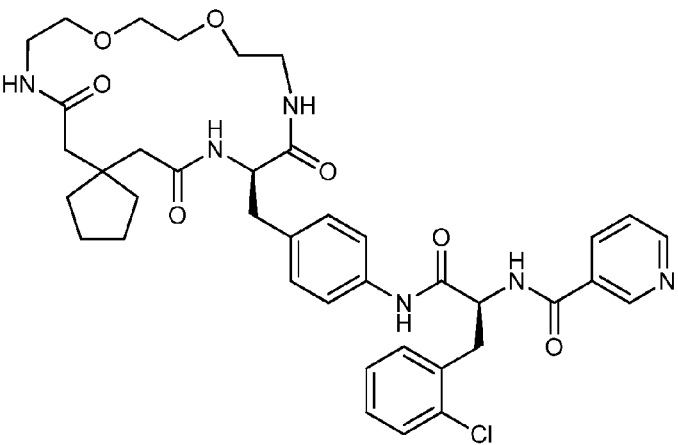
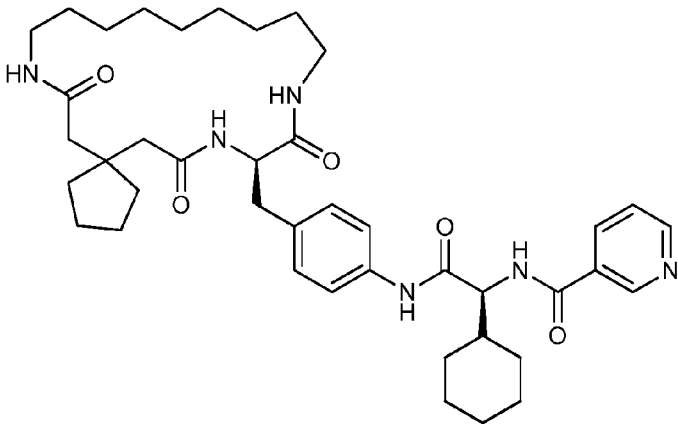
Compound No.	Structure
406	 <p>Chemical structure of Compound 406: A complex molecule featuring a 1,3-bis(2-oxoethyl)propan-2-ylidene-5-oxotetrahydro-2H-pyran-4-ylidene moiety. This moiety is linked via an amide bond to a 4-(2-chlorophenyl)phenyl group, which is further connected to a 2-(pyridin-4-yl)ethyl group. The structure includes a cyclopentyl ring and a chlorine atom on the phenyl ring.</p>
407	 <p>Chemical structure of Compound 407: A complex molecule featuring a 1,3-bis(2-oxoethyl)propan-2-ylidene-5-oxotetrahydro-2H-pyran-4-ylidene moiety. This moiety is linked via an amide bond to a 4-(cyclohexyl)phenyl group, which is further connected to a 2-(pyridin-4-yl)ethyl group. The structure includes a cyclopentyl ring and a cyclohexyl ring.</p>

FIG. 12-138

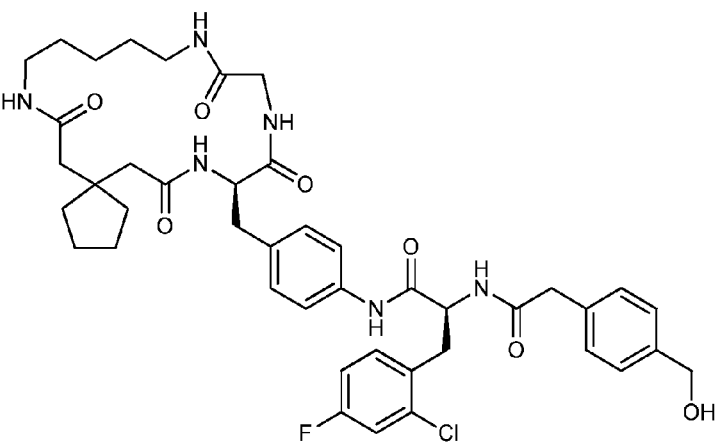
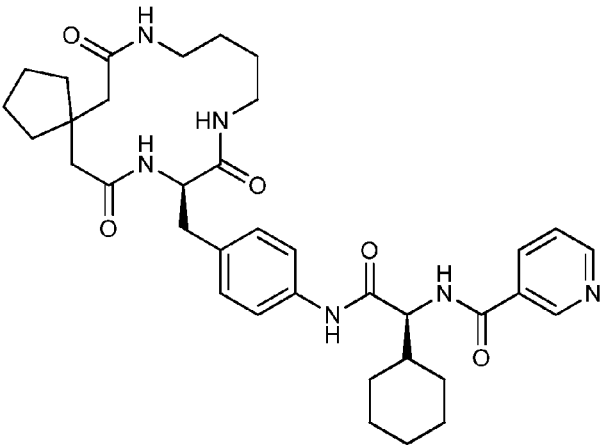
Compound No.	Structure
408	 <p>Chemical structure of Compound 408: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain includes a 4-hydroxybenzyl group and a 2-chloro-4-fluorophenyl group. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>
409	 <p>Chemical structure of Compound 409: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain includes a 4-pyridylmethyl group and a cyclohexyl group. The structure is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>

FIG. 12-139

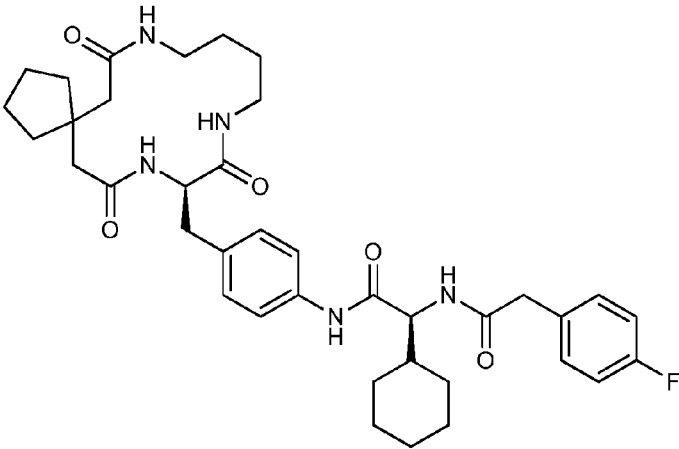
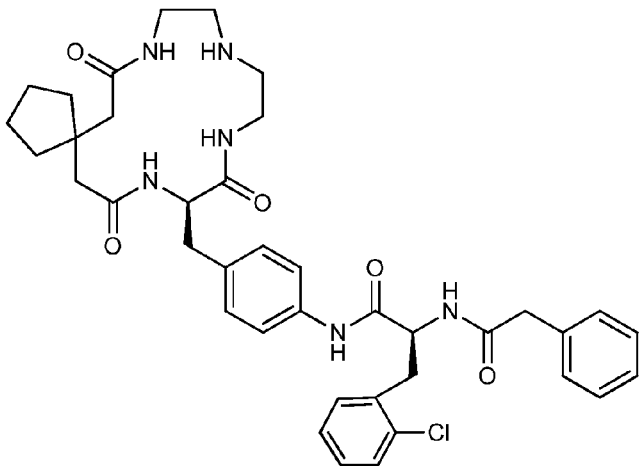
Compound No.	Structure
410	 <p>Chemical structure of Compound 410: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a cyclohexyl group and an amide linkage to a 4-fluorophenyl group.</p>
411	 <p>Chemical structure of Compound 411: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a 2-chlorophenyl group and an amide linkage to a benzyl group.</p>

FIG. 12-140

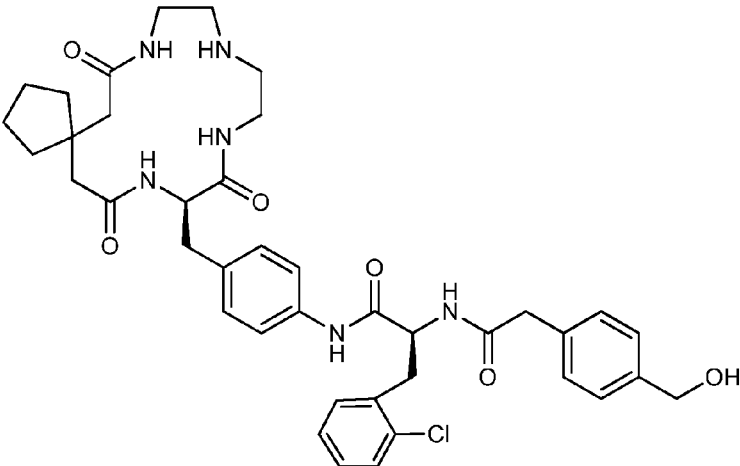
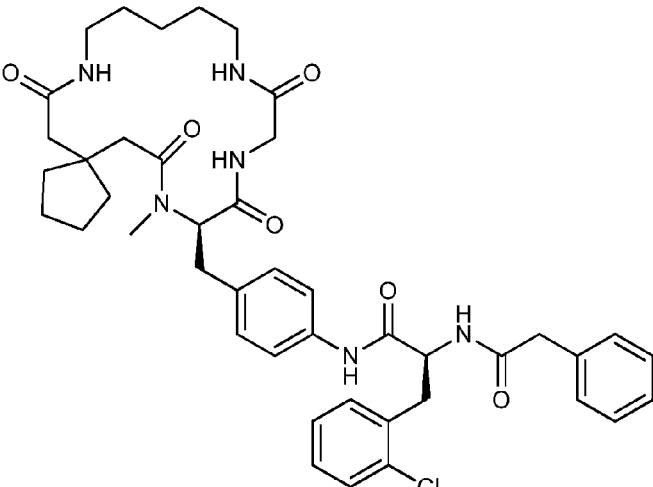
Compound No.	Structure
412	 <p>Chemical structure of Compound 412: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two NH groups and two carbonyl groups). This system is linked via an amide bond to a phenyl ring. The phenyl ring is further connected to a chiral center (marked with a wedge bond) which is part of a chain containing another amide bond, a 2-chlorophenyl group, and a final amide bond leading to a 4-hydroxybenzyl group.</p>
413	 <p>Chemical structure of Compound 413: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two NH groups and two carbonyl groups). This system is linked via an amide bond to a phenyl ring. The phenyl ring is further connected to a chiral center (marked with a wedge bond) which is part of a chain containing another amide bond, a 2-chlorophenyl group, and a final amide bond leading to a benzyl group.</p>

FIG. 12-141

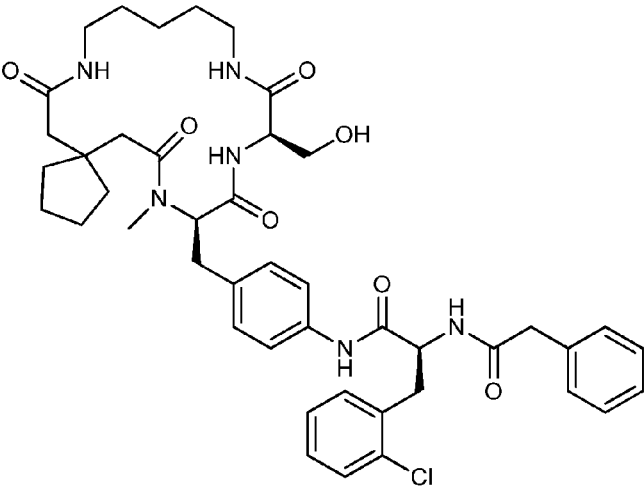
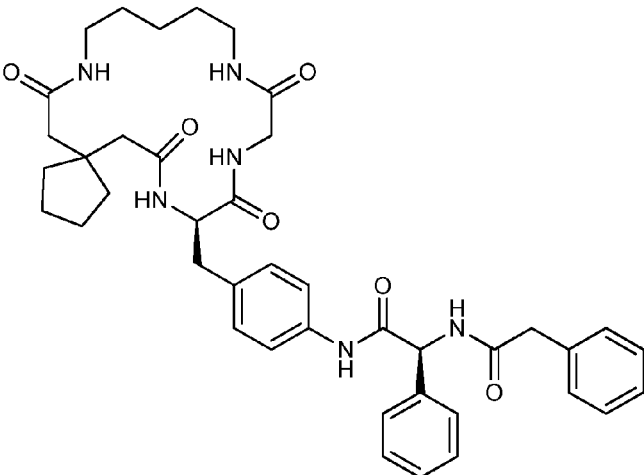
Compound No.	Structure
414	 <p>Chemical structure of compound 414. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a nitrogen atom). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a chiral center that is part of a side chain containing a hydroxyl group and a benzamide group. The side chain also includes a long-chain amide and a benzamide group.</p>
415	 <p>Chemical structure of compound 415. It is similar to compound 414, but the side chain is modified, lacking the hydroxyl group and the long-chain amide. The structure shows a bicyclic amide system linked to a benzamide moiety, which is further connected to a chiral center that is part of a side chain containing a benzamide group.</p>

FIG. 12-142

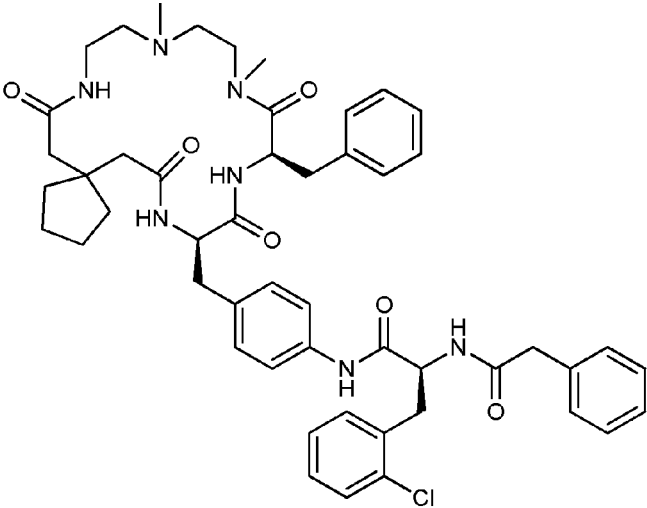
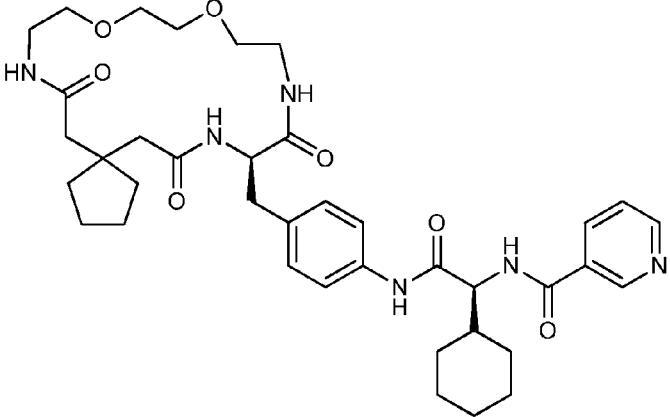
Compound No.	Structure
416	 <p>Chemical structure of Compound 416: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide structure. The right side features a benzyl group attached to a carbonyl group, which is also part of an amide structure. The molecule includes several amide bonds and a tertiary amine group.</p>
417	 <p>Chemical structure of Compound 417: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide structure. The right side features a benzyl group attached to a carbonyl group, which is also part of an amide structure. The molecule includes several amide bonds and a tertiary amine group.</p>

FIG. 12-143

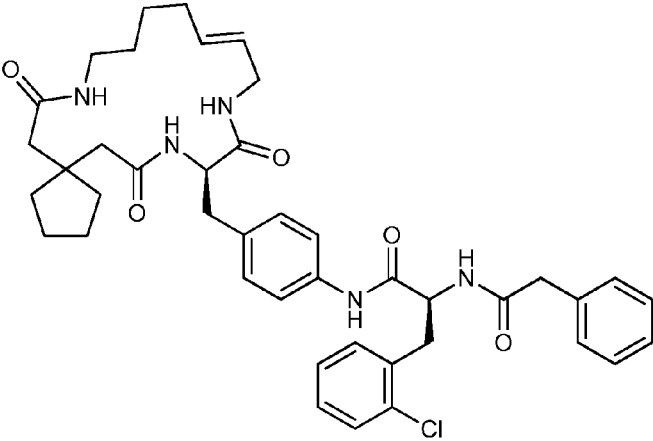
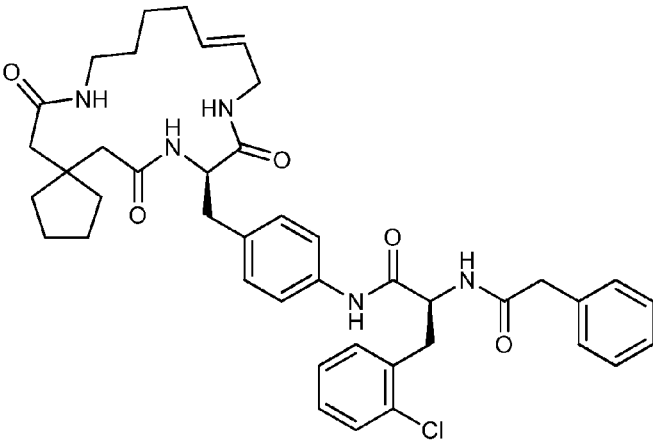
Compound No.	Structure
418	 <p>Chemical structure of Compound 418. It features a complex polycyclic amide system. A cyclopentane ring is fused to a six-membered ring containing two amide groups (NH). This system is linked via a methylene bridge to a benzene ring. The benzene ring is further connected to a six-membered ring containing a carbonyl group and an amide group (NH). This amide group is linked to a benzyl group, which is connected to a benzene ring. The benzene ring is further connected to a benzyl group, which is connected to a benzene ring. The benzene ring is further connected to a benzyl group, which is connected to a benzene ring.</p>
419	 <p>Chemical structure of Compound 419. It is similar to Compound 418, but the amide group (NH) in the six-membered ring is replaced by a nitrogen atom (N) with a hydrogen atom (H) attached, forming a secondary amine.</p>

FIG. 12-144

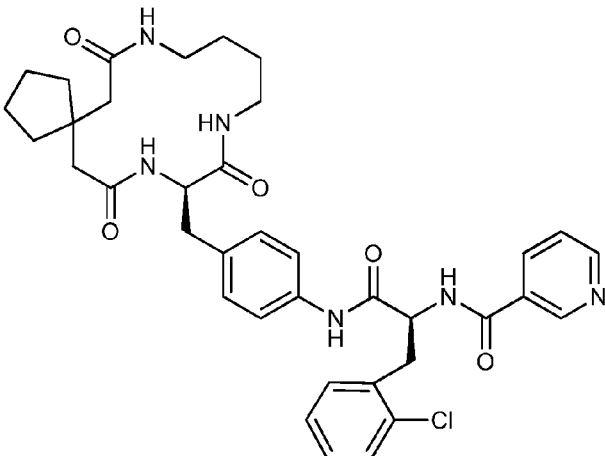
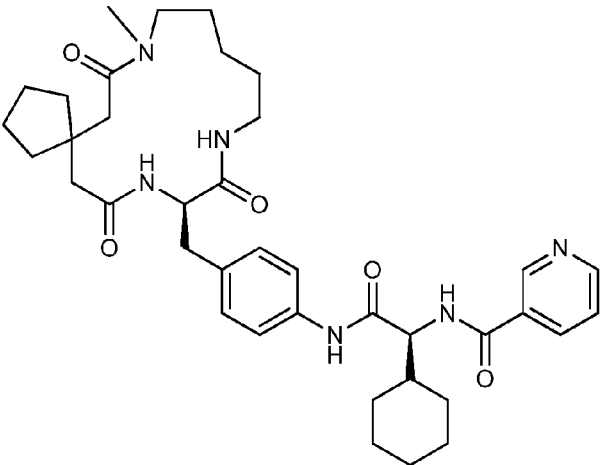
Compound No.	Structure
420	 <p>Chemical structure of Compound 420: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring) connected via an amide linkage to a chiral center. This chiral center is further connected to a benzene ring, which is linked to another amide group. The final amide group is connected to a chiral center that is also linked to a benzene ring with a chlorine substituent and a pyridine ring.</p>
421	 <p>Chemical structure of Compound 421: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring) connected via an amide linkage to a chiral center. This chiral center is further connected to a benzene ring, which is linked to another amide group. The final amide group is connected to a chiral center that is also linked to a benzene ring and a cyclohexane ring.</p>

FIG. 12-145

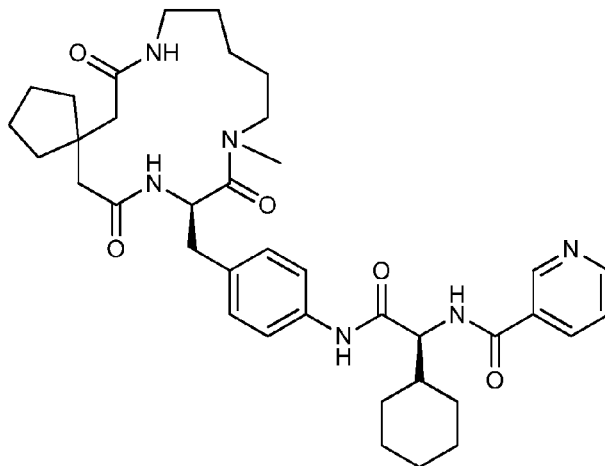
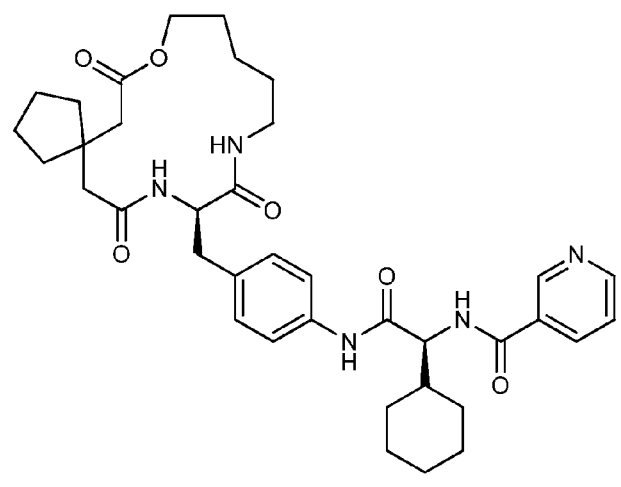
Compound No.	Structure
422	 <p>Chemical structure of Compound 422: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group, which is part of a larger amide-containing chain. This chain includes a benzamide moiety, a cyclohexyl group, and a pyridine ring.</p>
423	 <p>Chemical structure of Compound 423: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group, which is part of a larger amide-containing chain. This chain includes a benzamide moiety, a cyclohexyl group, and a pyridine ring.</p>

FIG. 12-146

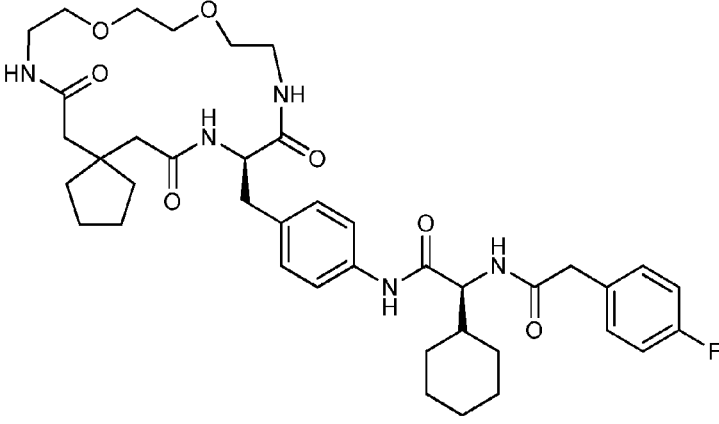
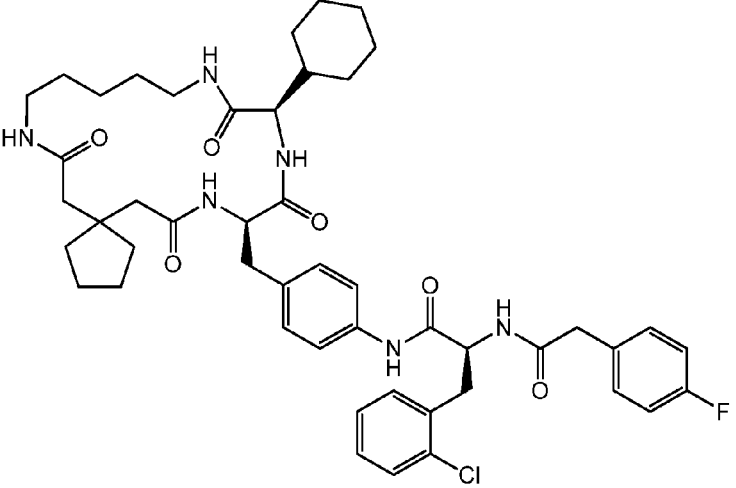
Compound No.	Structure
424	 <p>Chemical structure of Compound 424: A complex molecule featuring a 1,3-bis(2-oxoethyl)-5-oxa-7-azabicyclo[3.3.1]nonane core. One of the 2-oxoethyl groups is substituted with a cyclopentylmethyl group. The other 2-oxoethyl group is substituted with a 1-((4-((4-fluorophenyl)amino)-4-oxobutyl)amino)cyclohexylmethyl group.</p>
425	 <p>Chemical structure of Compound 425: A complex molecule featuring a 1,3-bis(2-oxoethyl)-5-oxa-7-azabicyclo[3.3.1]nonane core. One of the 2-oxoethyl groups is substituted with a cyclopentylmethyl group. The other 2-oxoethyl group is substituted with a 1-((4-((4-fluorophenyl)amino)-4-oxobutyl)amino)-2-chlorophenylmethyl group. Additionally, the 5-oxa-7-azabicyclo[3.3.1]nonane core is substituted with a 1-cyclohexyl-2-oxoethyl group.</p>

FIG. 12-147

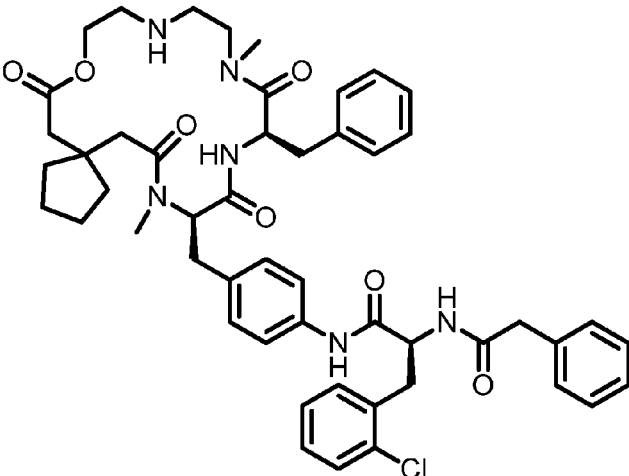
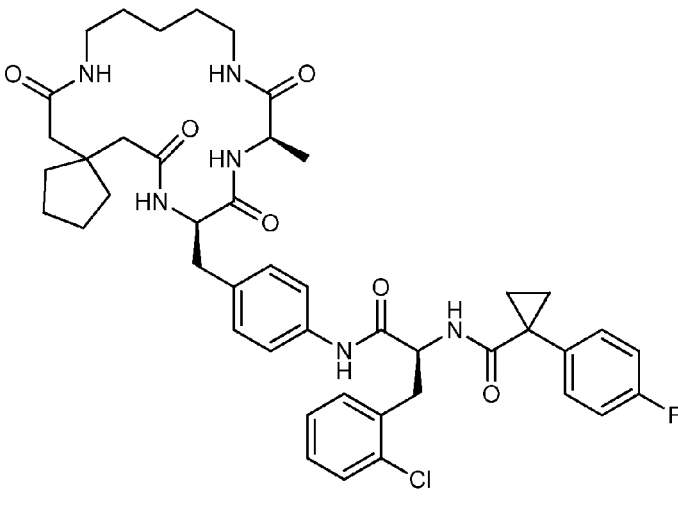
Compound No.	Structure
426	 <p>Chemical structure of Compound 426: A complex molecule featuring a cyclopentane ring substituted with a methylamino group and a side chain containing a carbamate, a benzyl group, and a 2-chlorophenyl moiety. The side chain also includes a 2-chlorophenyl group and a benzyl group.</p>
427	 <p>Chemical structure of Compound 427: A complex molecule featuring a cyclopentane ring substituted with a methylamino group and a side chain containing a carbamate, a benzyl group, and a 2-chlorophenyl moiety. The side chain also includes a 2-chlorophenyl group and a benzyl group.</p>

FIG. 12-148

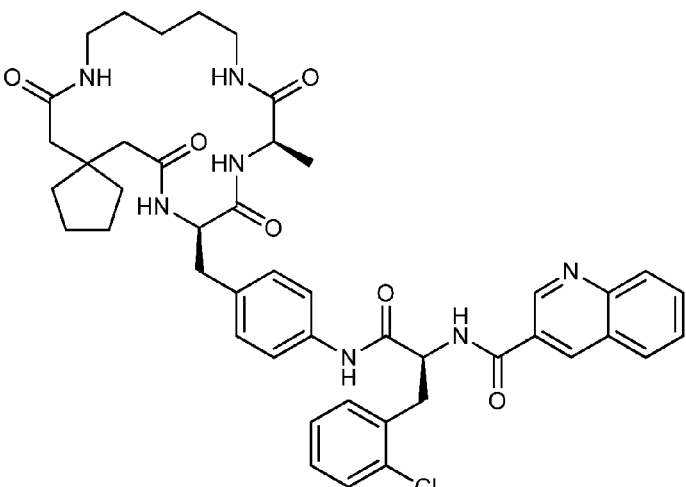
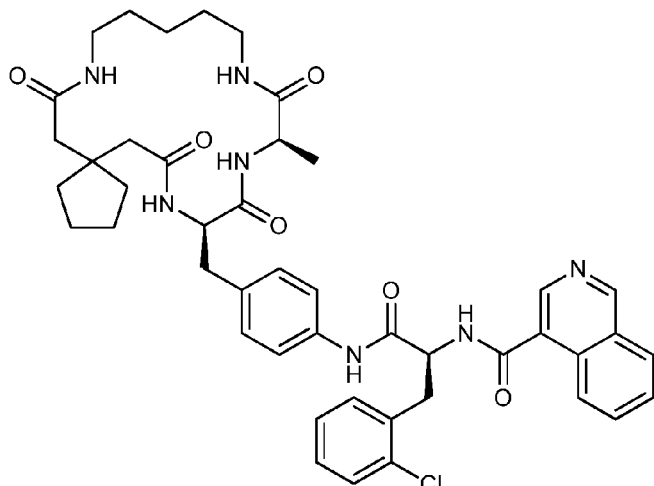
Compound No.	Structure
428	 <p>Chemical structure of Compound 428. It features a macrocyclic amide ring (12-membered) with a cyclopentyl group and a methyl group. The macrocycle is linked via an amide bond to a side chain containing a 4-phenyl group, a 2-chlorophenyl group, and a quinoline-2-carboxamide group.</p>
429	 <p>Chemical structure of Compound 429. It is similar to Compound 428, but the side chain is modified, featuring a 4-phenyl group, a 2-chlorophenyl group, and a quinoline-2-carboxamide group, with a different stereochemistry at the chiral center.</p>

FIG. 12-149

Compound No.	Structure
430	
431	

FIG. 12-150

[illegible]

FIG. 12-151

Compound No.	Structure
434	
435	

FIG. 12-152

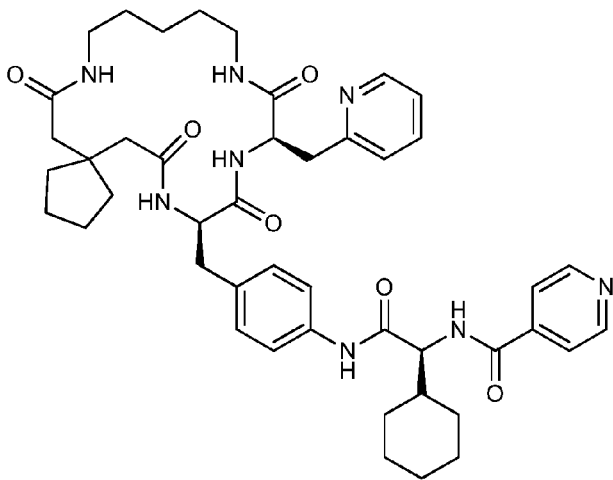
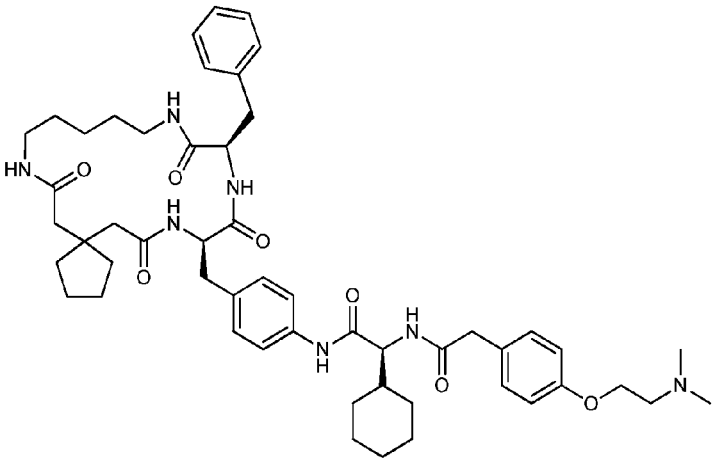
Compound No.	Structure
436	 <p>Chemical structure of Compound 436: A complex molecule featuring a central chiral center (C1) bonded to a cyclopentyl group, a benzyl group, and a pyridine-2-ylmethyl group. The benzyl group is further substituted with a pyridine-2-ylmethyl group. The pyridine-2-ylmethyl group is further substituted with a cyclohexyl group. The pyridine-2-ylmethyl group is further substituted with a pyridine-2-ylmethyl group.</p>
437	 <p>Chemical structure of Compound 437: A complex molecule featuring a central chiral center (C1) bonded to a cyclopentyl group, a benzyl group, and a pyridine-2-ylmethyl group. The benzyl group is further substituted with a pyridine-2-ylmethyl group. The pyridine-2-ylmethyl group is further substituted with a cyclohexyl group. The pyridine-2-ylmethyl group is further substituted with a pyridine-2-ylmethyl group.</p>

FIG. 12-153

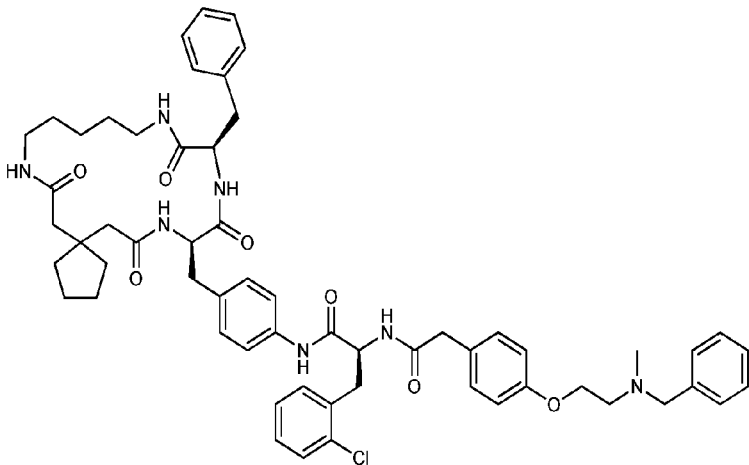
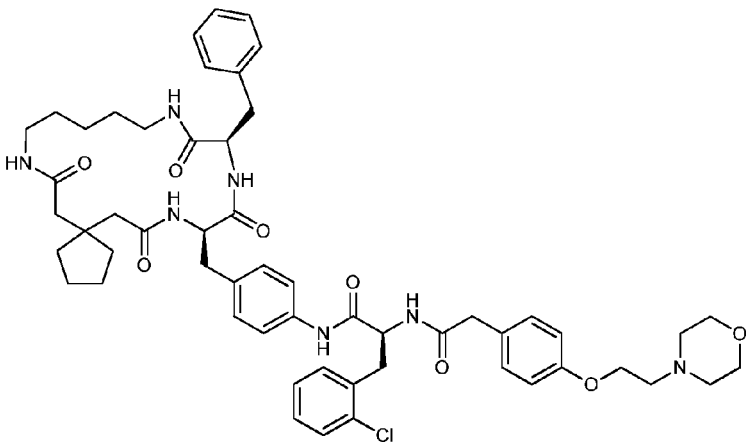
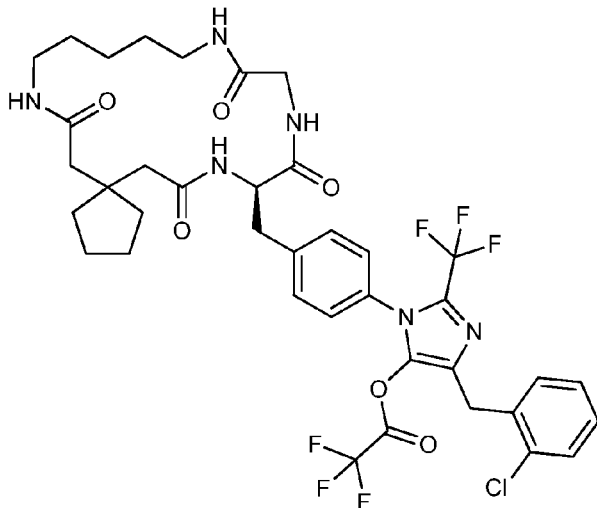
Compound No.	Structure
438	
439	
440	

FIG. 12-154

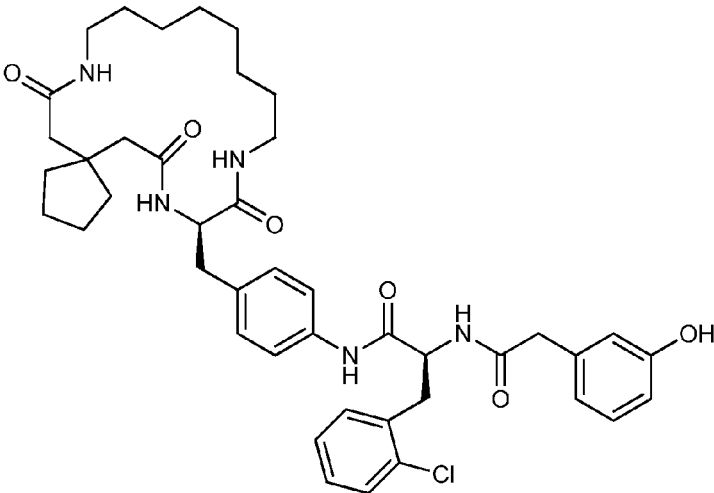
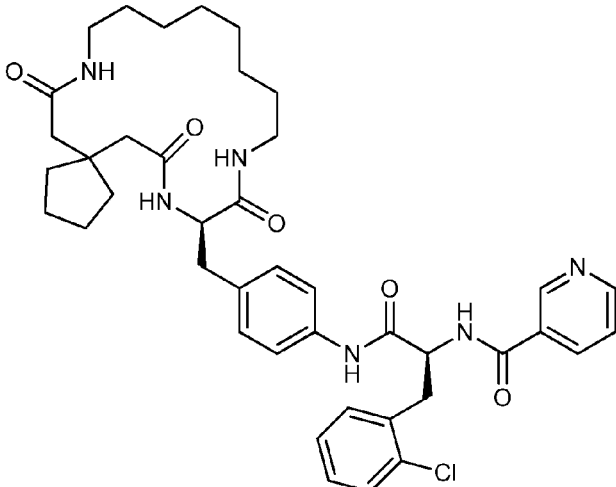
Compound No.	Structure
441	 <p>Chemical structure of Compound 441: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide group). This system is linked via a chiral center to a chain containing a benzamide moiety, a chiral center, and a 4-hydroxyphenyl group.</p>
442	 <p>Chemical structure of Compound 442: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide group). This system is linked via a chiral center to a chain containing a benzamide moiety, a chiral center, and a pyridine-2-ylmethyl group.</p>

FIG. 12-155

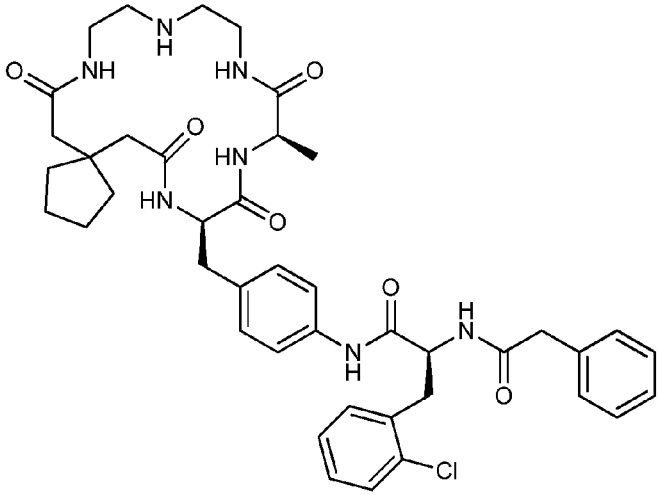
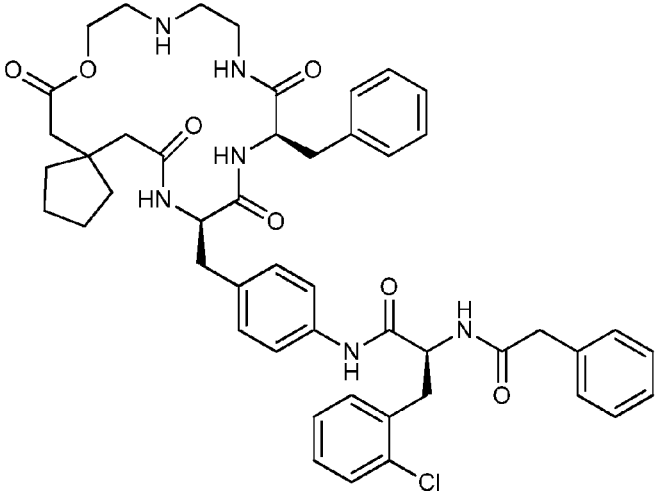
Compound No.	Structure
443	 <p>Chemical structure of Compound 443. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a nitrogen atom). This system is linked via an amide bond to a chiral center, which is further connected to a benzyl group. The benzyl group is attached to a para-substituted benzene ring. This benzene ring is linked via an amide bond to another chiral center, which is connected to a benzyl group with a chlorine substituent at the ortho position. Finally, this chiral center is linked via an amide bond to a third chiral center, which is connected to a benzyl group.</p>
444	 <p>Chemical structure of Compound 444. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a nitrogen atom). This system is linked via an amide bond to a chiral center, which is further connected to a benzyl group. The benzyl group is attached to a para-substituted benzene ring. This benzene ring is linked via an amide bond to another chiral center, which is connected to a benzyl group with a chlorine substituent at the ortho position. Finally, this chiral center is linked via an amide bond to a third chiral center, which is connected to a benzyl group.</p>

FIG. 12-156

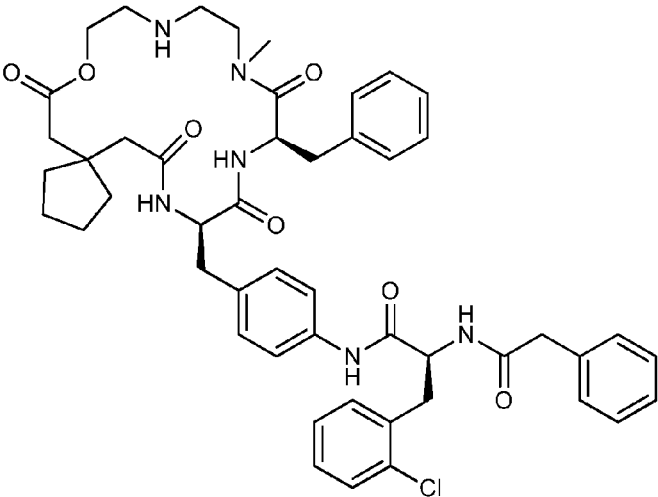
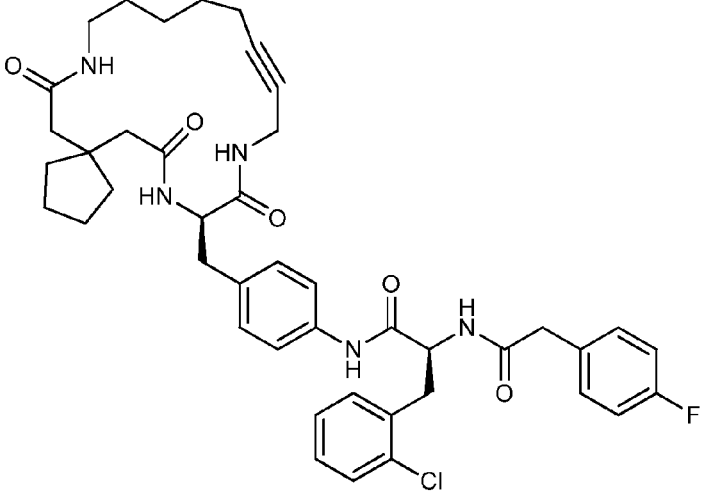
Compound No.	Structure
445	 <p>Chemical structure of Compound 445. It features a cyclopentane ring substituted with a carboxylate group and a side chain containing multiple amide and ester linkages. The side chain includes a benzyl group, a 4-chlorophenyl group, and a 4-phenylbutanamide moiety.</p>
446	 <p>Chemical structure of Compound 446. It features a cyclopentane ring substituted with a carboxylate group and a side chain containing multiple amide and ester linkages. The side chain includes a benzyl group, a 4-chlorophenyl group, and a 4-(4-fluorophenyl)butanamide moiety.</p>

FIG. 12-157

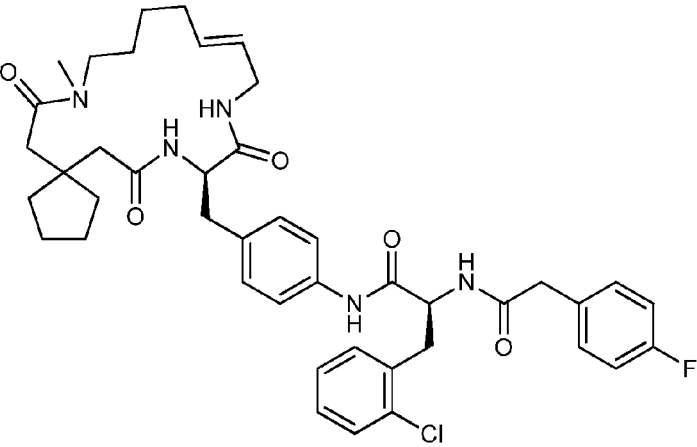
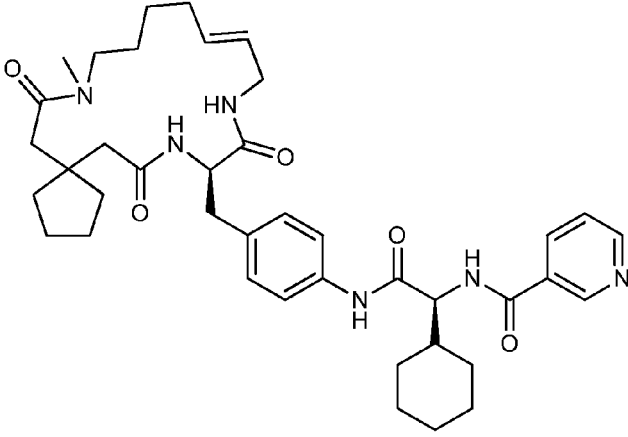
Compound No.	Structure
447	 <p>Chemical structure of Compound 447: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a nitrogen atom). This system is linked via an amide bond to a chiral center, which is further connected to a benzene ring. The benzene ring is part of a larger amide structure, which is linked to another chiral center. This second chiral center is connected to a third amide group, which is linked to a 4-fluorophenyl group.</p>
448	 <p>Chemical structure of Compound 448: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing a nitrogen atom). This system is linked via an amide bond to a chiral center, which is further connected to a benzene ring. The benzene ring is part of a larger amide structure, which is linked to another chiral center. This second chiral center is connected to a third amide group, which is linked to a pyridine ring.</p>

FIG. 12-158

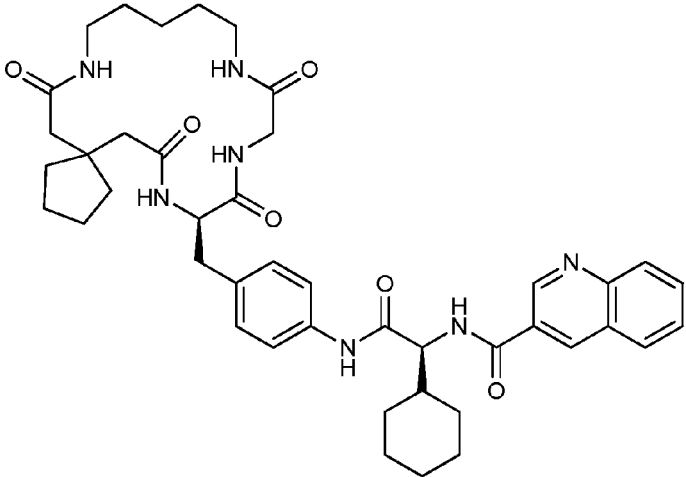
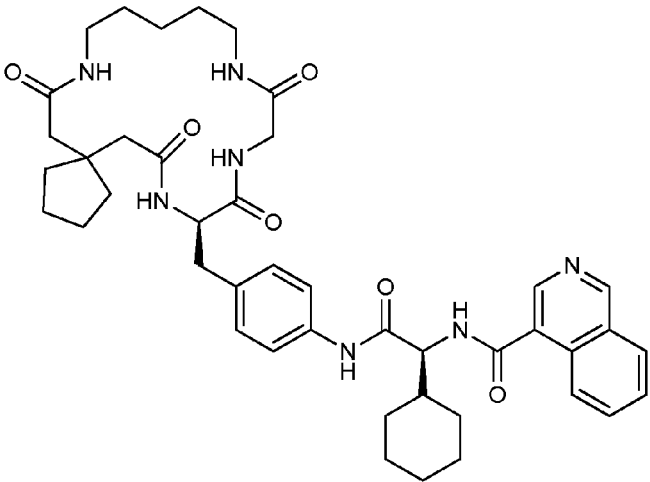
Compound No.	Structure
449	 <p>Chemical structure of Compound 449: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a chiral center (marked with a wedge bond) which is also attached to a cyclohexyl group. This chiral center is further linked to a benzamide moiety, which is connected to a quinoline ring system.</p>
450	 <p>Chemical structure of Compound 450: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a chiral center (marked with a wedge bond) which is also attached to a cyclohexyl group. This chiral center is further linked to a benzamide moiety, which is connected to a quinoline ring system.</p>

FIG. 12-159

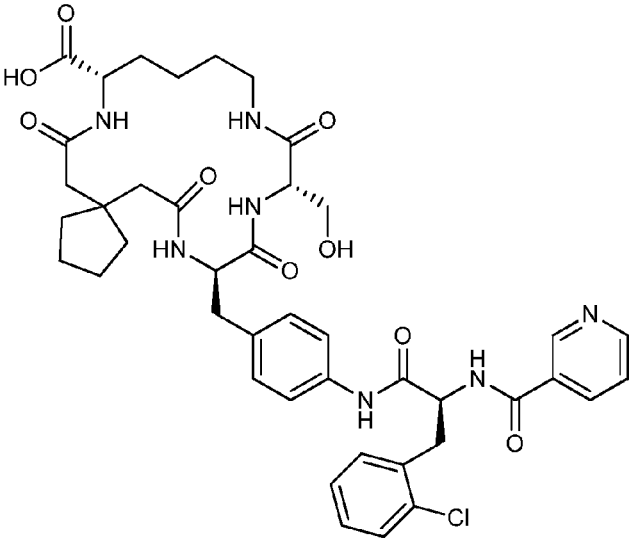
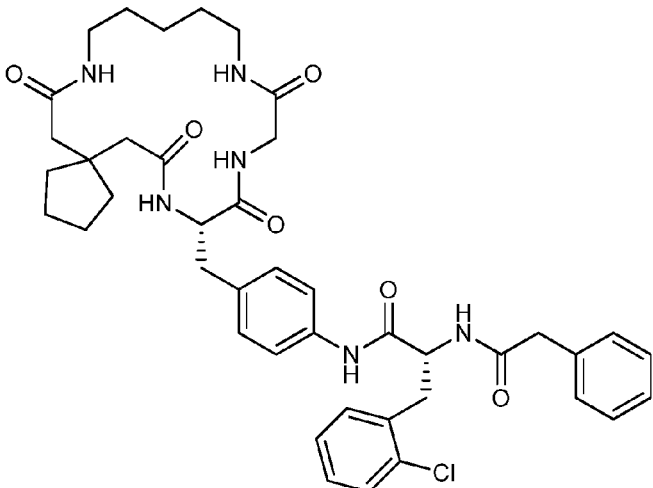
Compound No.	Structure
451	 <p>Chemical structure of Compound 451. It features a bicyclic amide core (a cyclopentane ring fused to a six-membered ring containing two amide groups). This core is linked via a chiral center to a side chain containing a p-phenylene ring, a 2-chlorophenyl ring, and a pyridine ring. Stereochemistry is indicated with wedges and dashes.</p>
452	 <p>Chemical structure of Compound 452. It features a bicyclic amide core similar to Compound 451. This core is linked via a chiral center to a side chain containing a p-phenylene ring, a 2-chlorophenyl ring, and a benzyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-160

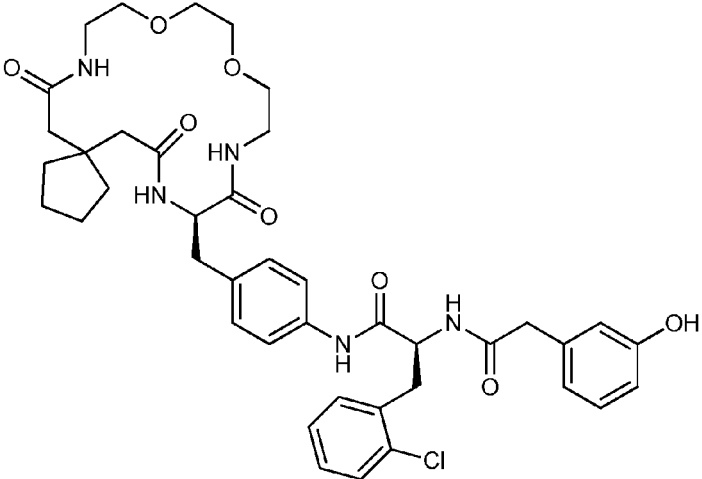
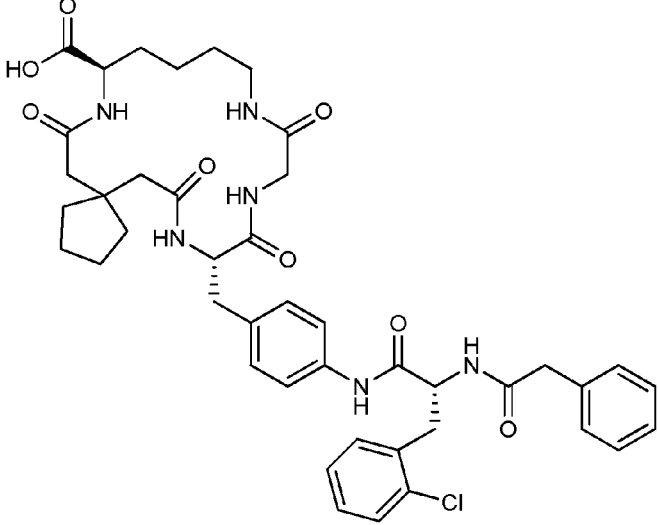
Compound No.	Structure
453	 <p>Chemical structure of Compound 453. It features a bicyclic amide core (a cyclopentane ring fused to a five-membered amide ring). This core is linked via an amide bond to a side chain containing a 4-(2-chlorophenyl)phenyl group, a 2-chlorophenyl group, and a 4-hydroxyphenyl group. The side chain also includes a 1,3-dioxolane ring system.</p>
454	 <p>Chemical structure of Compound 454. It features a bicyclic amide core (a cyclopentane ring fused to a five-membered amide ring). This core is linked via an amide bond to a side chain containing a 4-(2-chlorophenyl)phenyl group, a 2-chlorophenyl group, and a 4-phenylphenyl group. The side chain also includes a 1,3-dioxolane ring system.</p>

FIG. 12-161

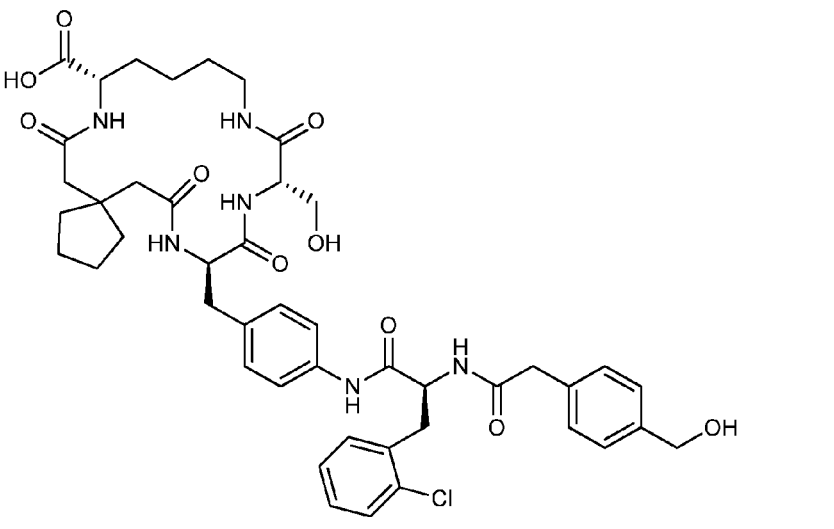
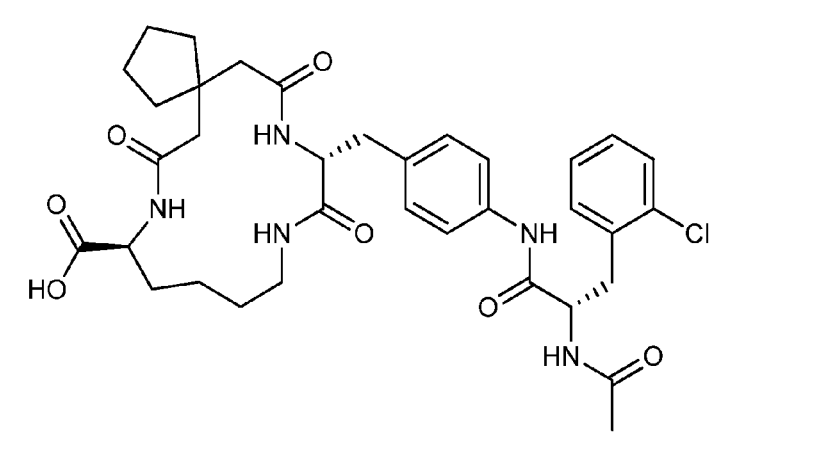
Compound No.	Structure
455	 <p>Chemical structure of Compound 455: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and an amide linkage. The amide chain continues through several amide bonds, including a 2-chlorophenyl group and a 4-hydroxybenzyl group. Stereochemistry is indicated with wedges and dashes.</p>
456	 <p>Chemical structure of Compound 456: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and an amide linkage. The amide chain continues through several amide bonds, including a 2-chlorophenyl group and a 4-hydroxybenzyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-162

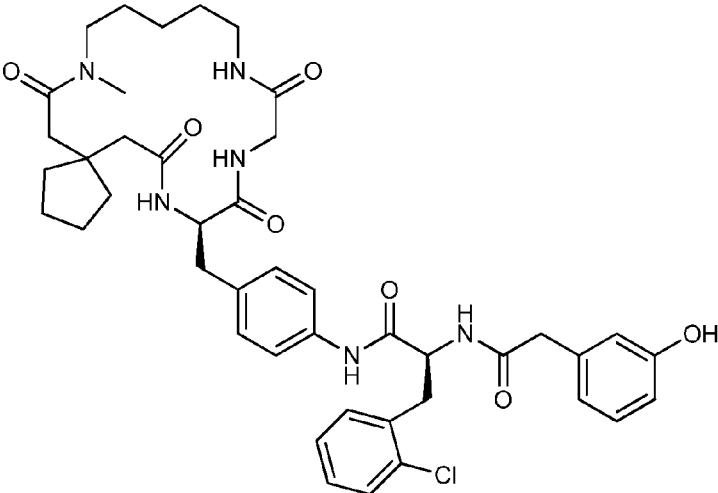
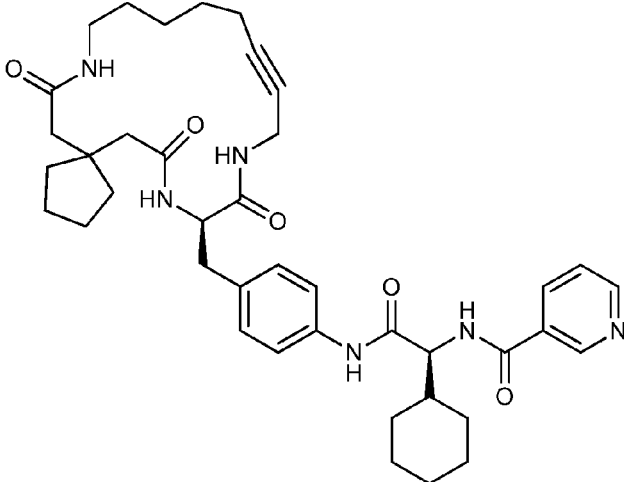
Compound No.	Structure
457	 <p>Chemical structure of compound 457: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with a nitrogen atom). This system is linked via an amide bond to a chain containing a benzene ring, a carbonyl group, and a chiral center. The chiral center is further linked to another amide bond, which is connected to a chain containing a carbonyl group, a benzene ring with a hydroxyl group, and a chlorine atom.</p>
458	 <p>Chemical structure of compound 458: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with a nitrogen atom). This system is linked via an amide bond to a chain containing a benzene ring, a carbonyl group, and a chiral center. The chiral center is further linked to another amide bond, which is connected to a chain containing a carbonyl group, a benzene ring with a nitrogen atom, and a cyclohexane ring.</p>

FIG. 12-163

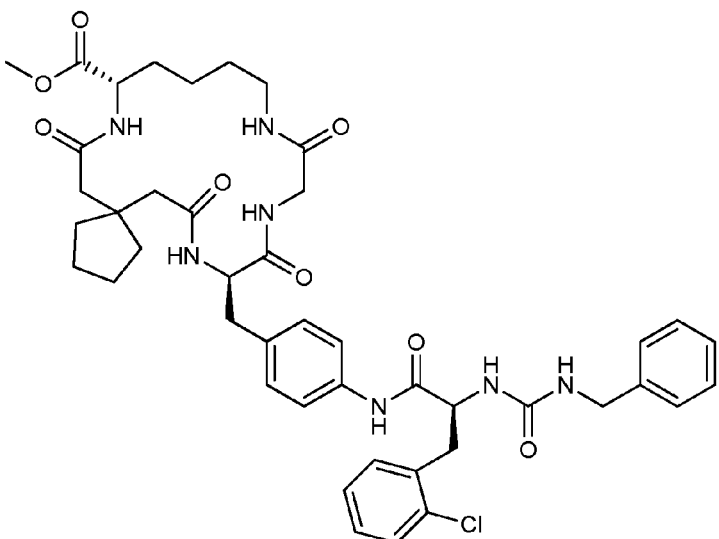
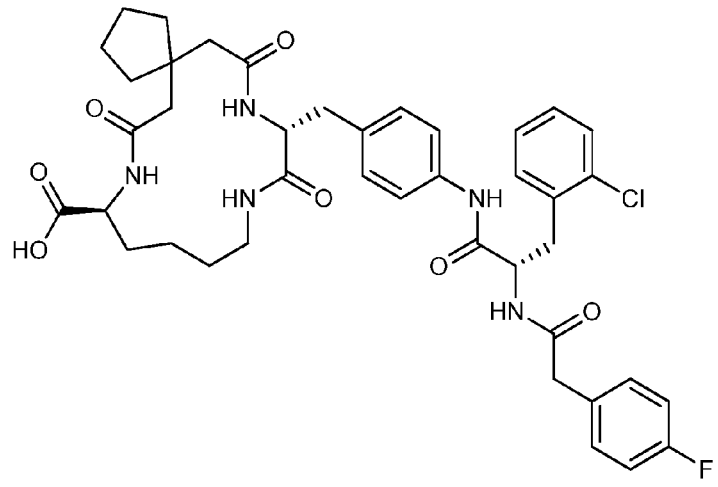
Compound No.	Structure
459	 <p>Chemical structure of Compound 459: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a methylene group to a benzene ring. The benzene ring is further substituted with an amide group connected to a chiral center, which is part of a chain containing another amide and a carbonyl group. The chain terminates in a benzyl group.</p>
460	 <p>Chemical structure of Compound 460: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a methylene group to a benzene ring. The benzene ring is further substituted with an amide group connected to a chiral center, which is part of a chain containing another amide and a carbonyl group. The chain terminates in a benzyl group.</p>

FIG. 12-164

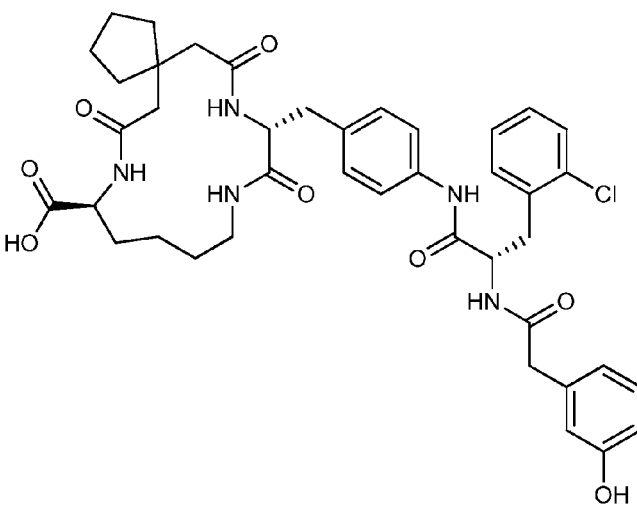
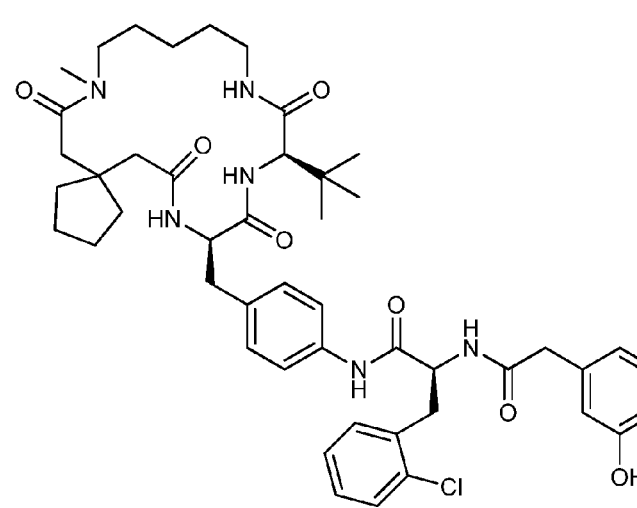
Compound No.	Structure
461	 <p>Chemical structure of Compound 461: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group and a carbamate group. The carbamate group is linked to a long chain containing several amide bonds. This chain is further substituted with a 4-chlorophenyl group, a 3-chlorophenyl group, and a 4-hydroxybenzyl group.</p>
462	 <p>Chemical structure of Compound 462: A complex molecule featuring a cyclopentane ring substituted with a carbamate group and a long chain containing several amide bonds. This chain is further substituted with a 4-chlorophenyl group, a 3-chlorophenyl group, and a 4-hydroxybenzyl group.</p>

FIG. 12-165

[illegible]

FIG. 12-166

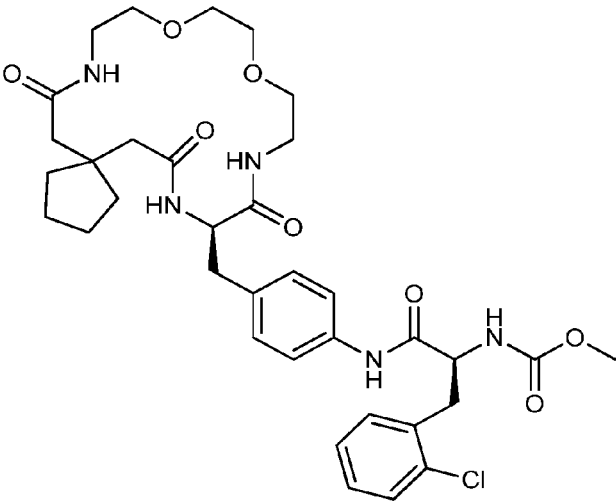
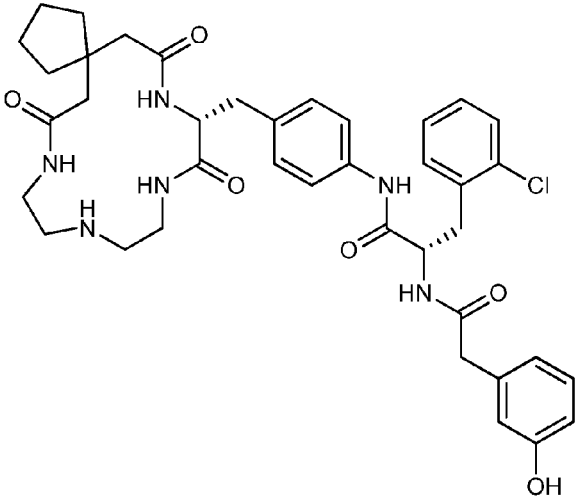
Compound No.	Structure
465	 <p>Chemical structure of Compound 465: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group). This is linked via a chiral center to a chain containing a benzamide moiety, a chiral center, and a methoxycarbonyl group. A 2-chlorophenyl group is also present.</p>
466	 <p>Chemical structure of Compound 466: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group). This is linked via a chiral center to a chain containing a benzamide moiety, a chiral center, and a 4-hydroxybenzamide moiety. A 2-chlorophenyl group is also present.</p>

FIG. 12-167

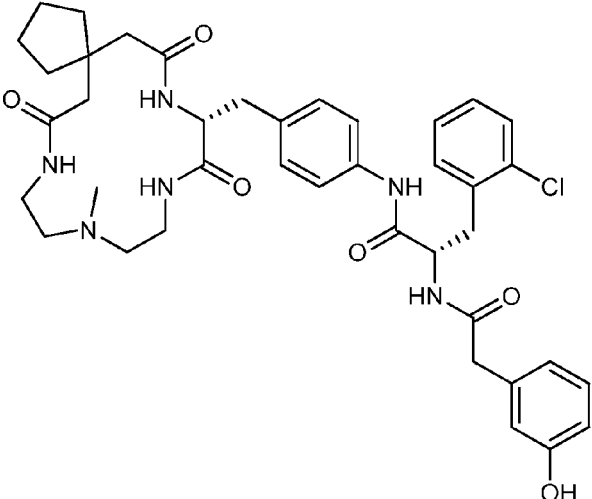
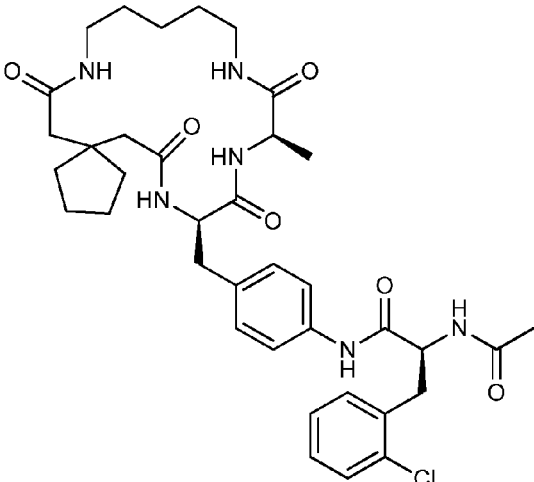
Compound No.	Structure
467	 <p>Chemical structure of Compound 467: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center (indicated by a dashed bond) to a para-substituted benzene ring. This benzene ring is further linked via an amide group to another chiral center (indicated by a dashed bond), which is connected to a 3-chlorophenyl group and a 4-hydroxybenzyl group.</p>
468	 <p>Chemical structure of Compound 468: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center (indicated by a dashed bond) to a para-substituted benzene ring. This benzene ring is further linked via an amide group to another chiral center (indicated by a dashed bond), which is connected to a 3-chlorophenyl group and an acetamido group.</p>

FIG. 12-168

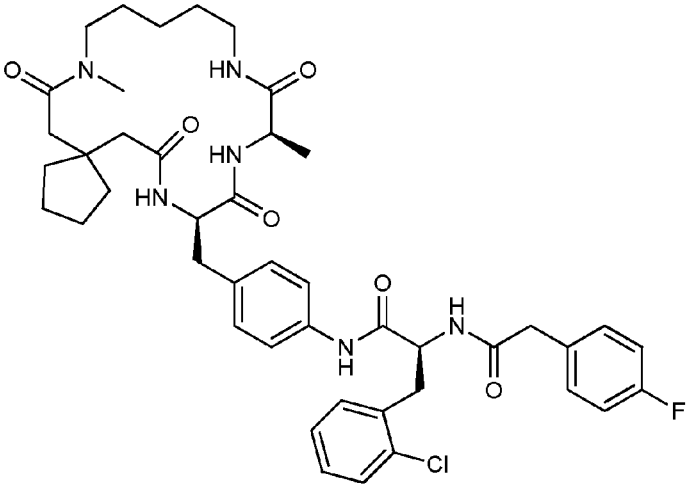
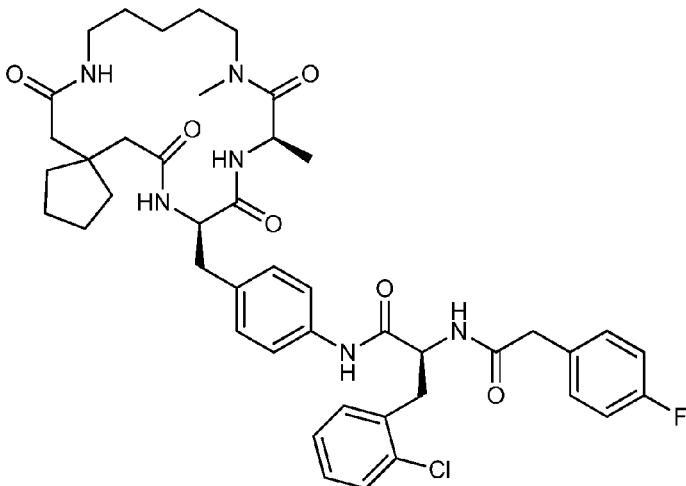
Compound No.	Structure
469	 <p>Chemical structure of Compound 469. It features a complex molecule with a central amide linkage. The left side includes a cyclopentyl ring and a long-chain amide. The right side includes a benzene ring with a chlorine substituent, a benzene ring with a fluorine substituent, and a long-chain amide.</p>
470	 <p>Chemical structure of Compound 470. It is similar to Compound 469, but the amide linkage on the left side is different, featuring a long-chain amide with a different branching pattern.</p>

FIG. 12-169

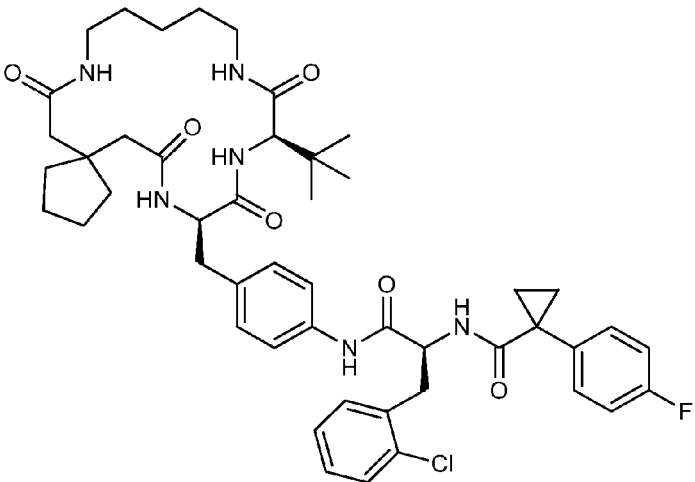
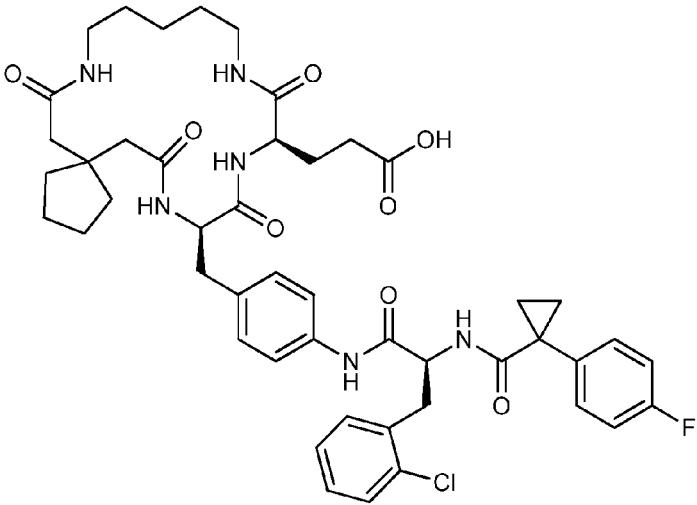
Compound No.	Structure
471	 <p>Chemical structure of Compound 471. It features a macrocyclic amide ring with a cyclopentyl group and a tert-butyl group. A side chain includes a benzyl group, a 2-chlorophenyl group, and a 4-fluorophenyl group connected via a cyclopropylmethyl amide linkage.</p>
472	 <p>Chemical structure of Compound 472. It is similar to Compound 471 but includes a carboxylic acid group at the end of the side chain instead of the 4-fluorophenyl group.</p>

FIG. 12-170

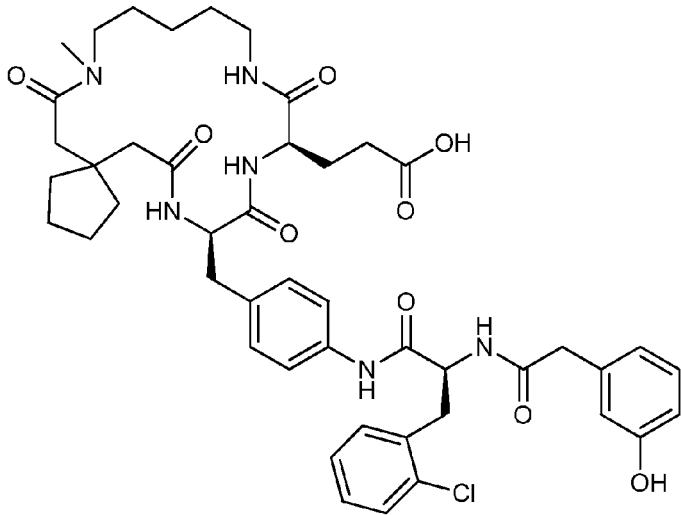
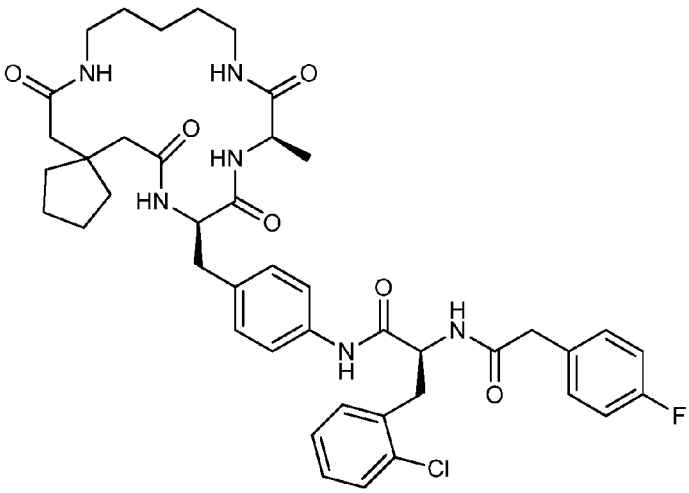
Compound No.	Structure
473	 <p>Chemical structure of compound 473. It features a complex molecule with a central amide linkage. The left side includes a cyclopentyl ring attached to a carbonyl group, which is part of a larger amide structure. The right side includes a carboxylic acid group, a benzene ring, and a chlorophenyl group. The structure is highly branched and contains multiple amide and ester functional groups.</p>
474	 <p>Chemical structure of compound 474. It is similar to compound 473 but with a different substituent on the right side. The structure includes a cyclopentyl ring, a carbonyl group, an amide linkage, a benzene ring, and a chlorophenyl group. The right side features a fluorophenyl group instead of a carboxylic acid group.</p>

FIG. 12-171

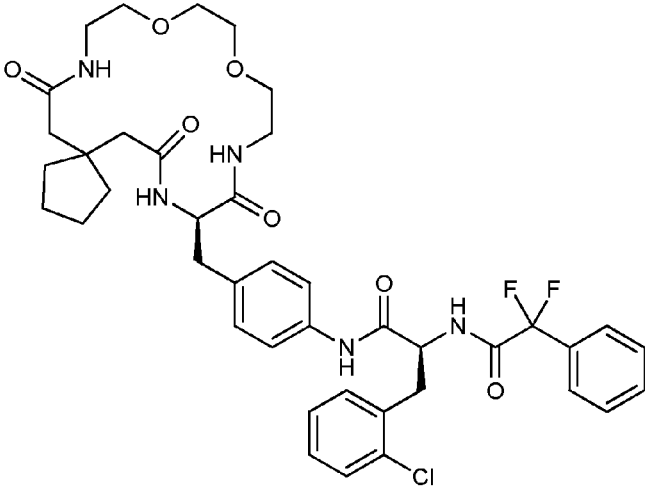
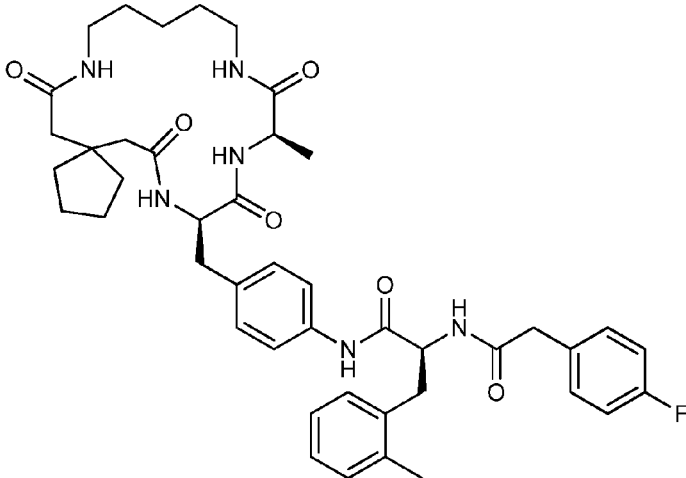
Compound No.	Structure
475	 <p>Chemical structure of Compound 475: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an NH group) linked via an amide bond to a chain containing a p-phenylene ring, a 2-chlorophenyl ring, and a 1,1-difluoro-2-phenylethan-1-yl group.</p>
476	 <p>Chemical structure of Compound 476: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an NH group) linked via an amide bond to a chain containing a p-phenylene ring, a 2-methylphenyl ring, and a 4-fluorophenyl group.</p>

FIG. 12-172

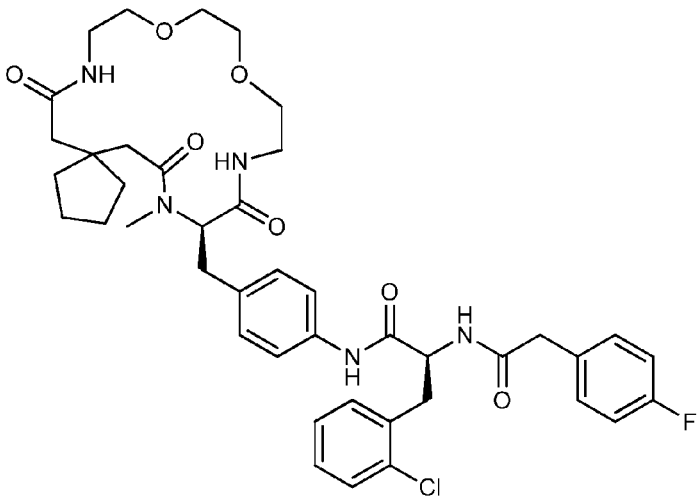
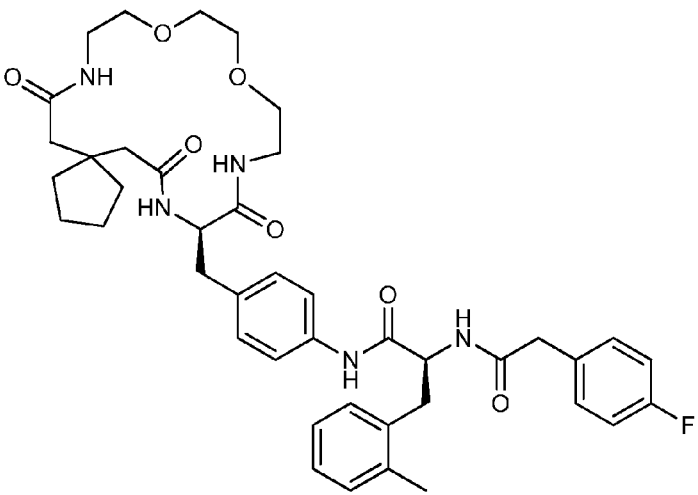
Compound No.	Structure
477	 <p>Chemical structure of Compound 477. It features a bicyclic amide core (a cyclopentane ring fused to a five-membered ring containing a nitrogen atom). This core is linked via a chiral center to a chain containing a benzamide group, a benzamide group, and a 4-fluorophenyl group. A 2-chlorophenyl group is also present in the chain.</p>
478	 <p>Chemical structure of Compound 478. It is similar to Compound 477, but the 2-chlorophenyl group is replaced by a 2-methylphenyl group.</p>

FIG. 12-173

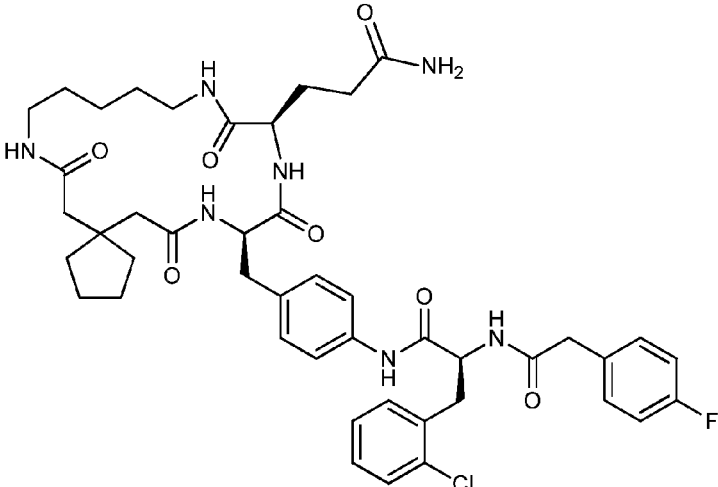
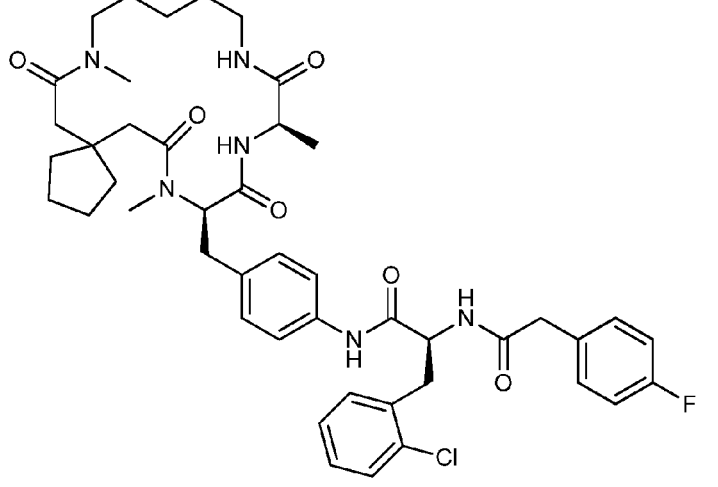
Compound No.	Structure
479	 <p>Chemical structure of Compound 479: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a long-chain amide. The right side features a 4-fluorophenyl group connected to a carbonyl group, which is further linked to a 2-chlorophenyl group. The structure also includes a 4-aminophenyl group and a 2-chlorophenyl group.</p>
480	 <p>Chemical structure of Compound 480: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a carbonyl group, which is further linked to a long-chain amide. The right side features a 4-fluorophenyl group connected to a carbonyl group, which is further linked to a 2-chlorophenyl group. The structure also includes a 4-aminophenyl group and a 2-chlorophenyl group.</p>

FIG. 12-174

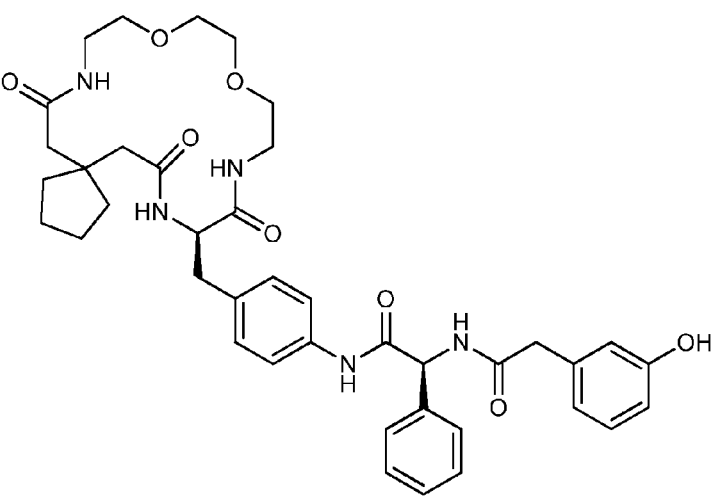
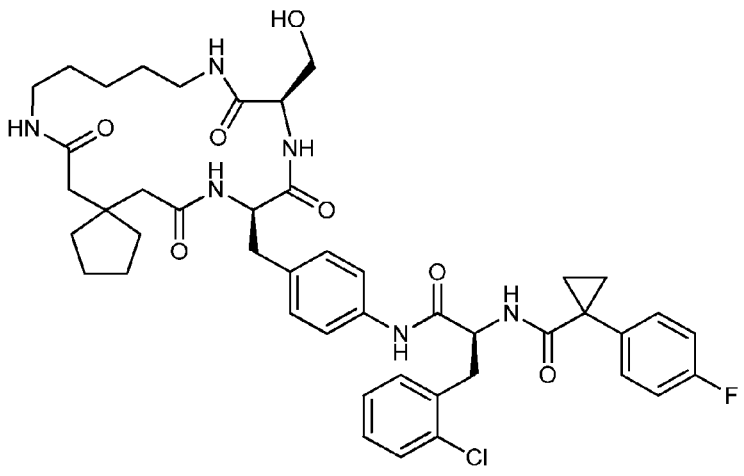
Compound No.	Structure
481	 <p>Chemical structure of Compound 481: A complex molecule featuring a cyclopentyl ring connected to a chain containing a morpholine ring, a carbonyl group, and a chiral center. The chain continues with a benzyl group, an amide linkage, a chiral center with a phenyl group, and another amide linkage to a 4-hydroxyphenyl group.</p>
482	 <p>Chemical structure of Compound 482: A complex molecule featuring a cyclopentyl ring connected to a chain containing a morpholine ring, a carbonyl group, and a chiral center. The chain continues with a benzyl group, an amide linkage, a chiral center with a 2-chlorophenyl group, and another amide linkage to a 4-fluorophenyl group.</p>

FIG. 12-175

Compound No.	Structure
483	
484	

FIG. 12-176

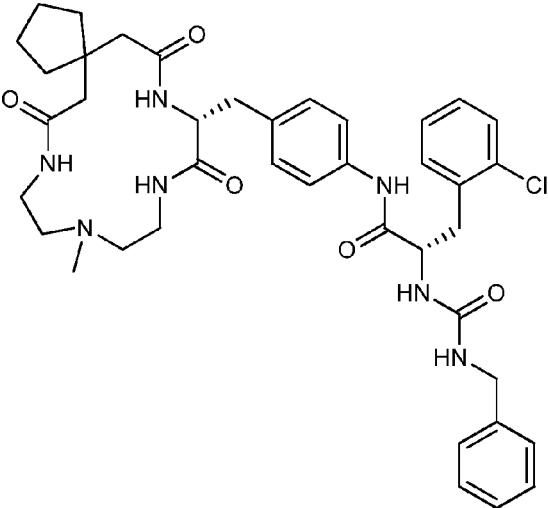
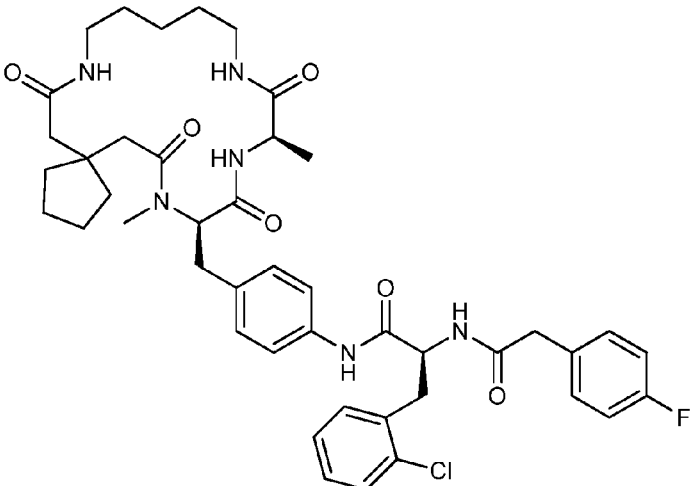
Compound No.	Structure
485	 <p>Chemical structure of Compound 485: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a nitrogen atom. The nitrogen is part of a chain that includes a carbonyl group, a chiral center (dashed bond), a benzene ring, a carbonyl group, a chiral center (dashed bond), a benzene ring with a chlorine substituent, a carbonyl group, a chiral center (dashed bond), a carbonyl group, and a benzyl group.</p>
486	 <p>Chemical structure of Compound 486: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a nitrogen atom. The nitrogen is part of a chain that includes a carbonyl group, a chiral center (wedged bond), a carbonyl group, a benzene ring, a carbonyl group, a chiral center (wedged bond), a carbonyl group, a benzene ring with a chlorine substituent, a carbonyl group, a chiral center (wedged bond), a carbonyl group, and a benzene ring with a fluorine substituent.</p>

FIG. 12-177

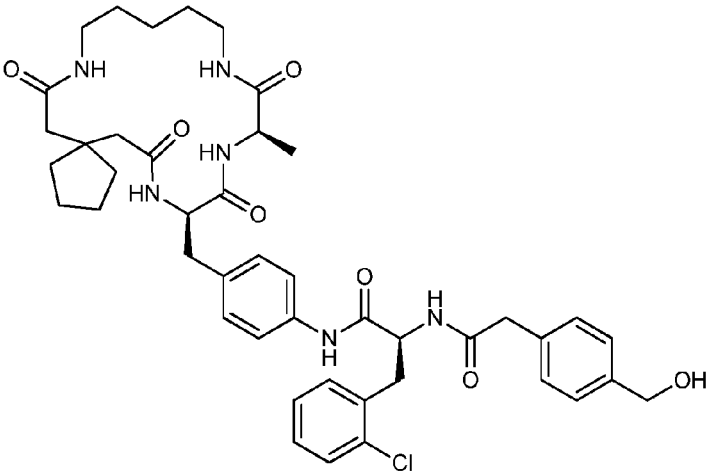
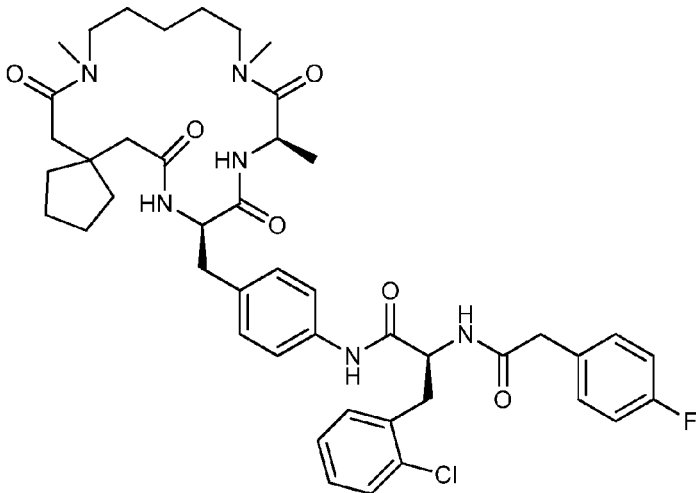
Compound No.	Structure
487	 <p>Chemical structure of Compound 487: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a chiral center (C1) which is also part of a 5-membered amide ring. C1 is further linked to a 4-chlorophenyl group. This 4-chlorophenyl group is connected via an amide bond to another chiral center (C2), which is part of a 5-membered amide ring. C2 is further linked to a 4-hydroxybenzyl group.</p>
488	 <p>Chemical structure of Compound 488: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a chiral center (C1) which is also part of a 5-membered amide ring. C1 is further linked to a 4-chlorophenyl group. This 4-chlorophenyl group is connected via an amide bond to another chiral center (C2), which is part of a 5-membered amide ring. C2 is further linked to a 4-fluorobenzyl group.</p>

FIG. 12-178

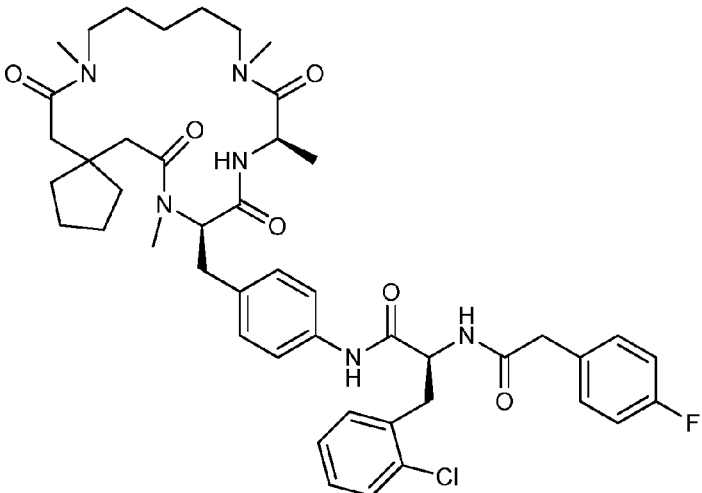
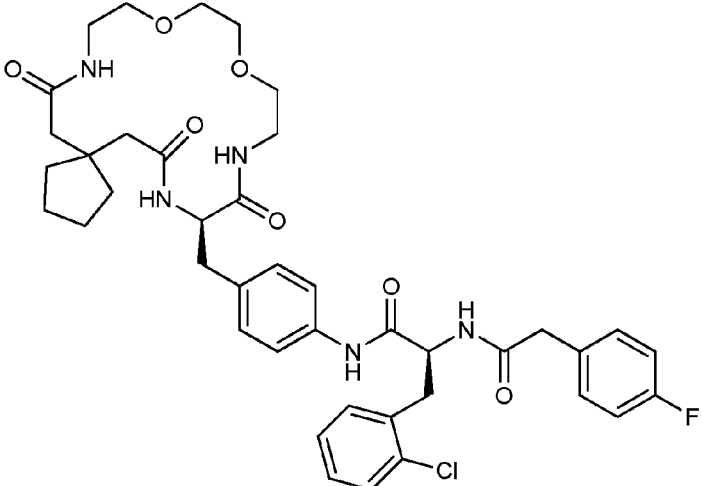
Compound No.	Structure
489	 <p>Chemical structure of Compound 489: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a pyrrolidine ring) connected via a linker to a 4-chlorophenyl group. This is further linked to a 4-fluorophenyl group through a series of amide and ether linkages.</p>
490	 <p>Chemical structure of Compound 490: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a pyrrolidine ring) connected via a linker to a 4-chlorophenyl group. This is further linked to a 4-fluorophenyl group through a series of amide and ether linkages.</p>

FIG. 12-179

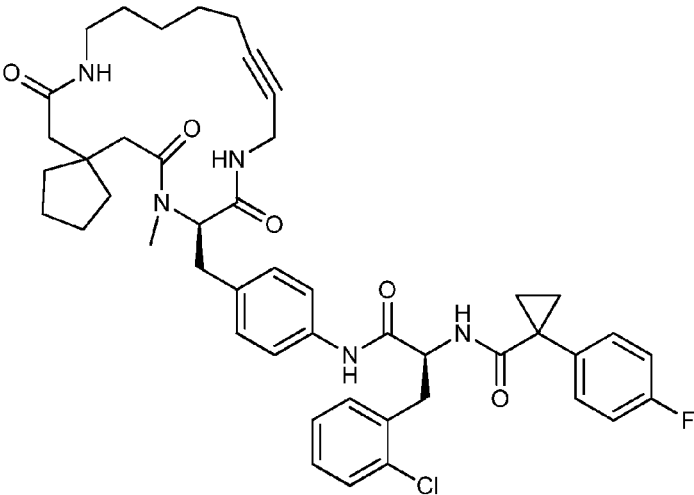
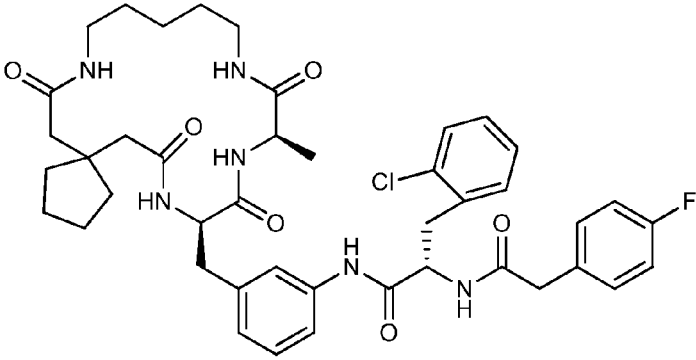
Compound No.	Structure
491	 <p>Chemical structure of Compound 491. It features a bicyclic amide system (cyclopentane fused to a six-membered ring with an NH group) connected via a methylene group to a chiral center. This chiral center is also bonded to a methyl group and a long chain containing an alkyne. The long chain continues through another amide linkage to a benzamide moiety, which is further connected to a chiral center. This second chiral center is bonded to a hydrogen atom and a group containing a cyclopropyl ring and a 4-fluorophenyl group.</p>
492	 <p>Chemical structure of Compound 492. It features a bicyclic amide system (cyclopentane fused to a six-membered ring with an NH group) connected via a methylene group to a chiral center. This chiral center is also bonded to a hydrogen atom and a group containing a cyclopropyl ring and a 4-fluorophenyl group. The structure is more complex than 491, with multiple amide linkages and a 2-chlorophenyl group.</p>

FIG. 12-180

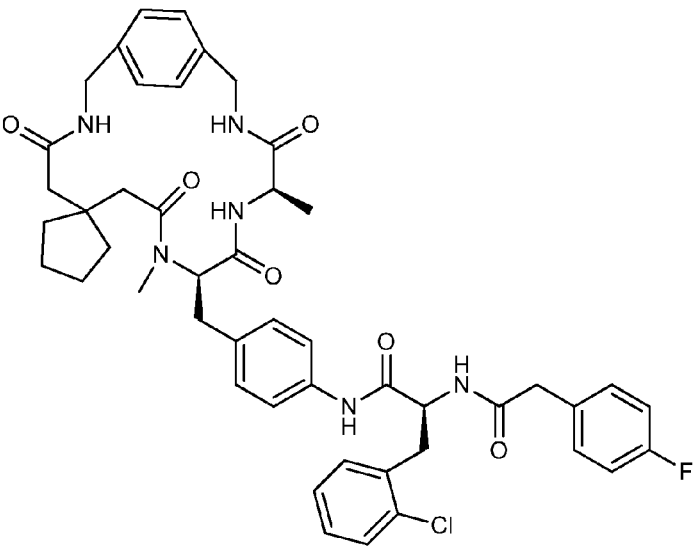
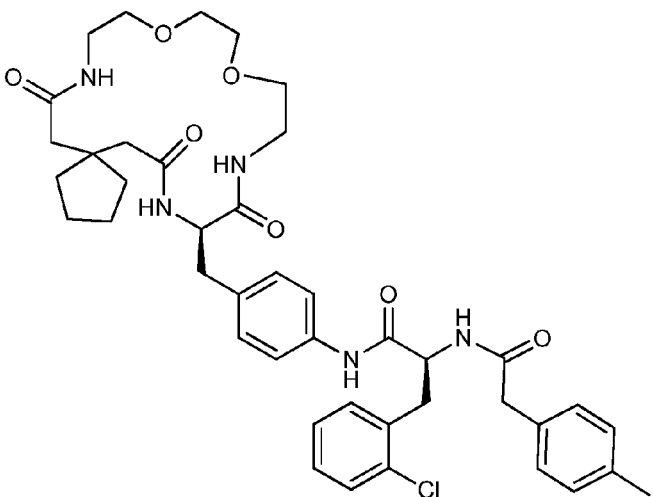
Compound No.	Structure
493	 <p>Chemical structure of Compound 493. The molecule features a central cyclopentane ring substituted with a carbonyl group and a nitrogen atom. The nitrogen is part of a complex amide system that includes a benzyl group, a p-toluenesulfonyl group, and a 4-fluorophenyl group. The structure is highly branched and contains multiple amide and ether linkages.</p>
494	 <p>Chemical structure of Compound 494. The molecule features a central cyclopentane ring substituted with a carbonyl group and a nitrogen atom. The nitrogen is part of a complex amide system that includes a benzyl group, a p-toluenesulfonyl group, and a 4-methylphenyl group. The structure is highly branched and contains multiple amide and ether linkages.</p>

FIG. 12-181

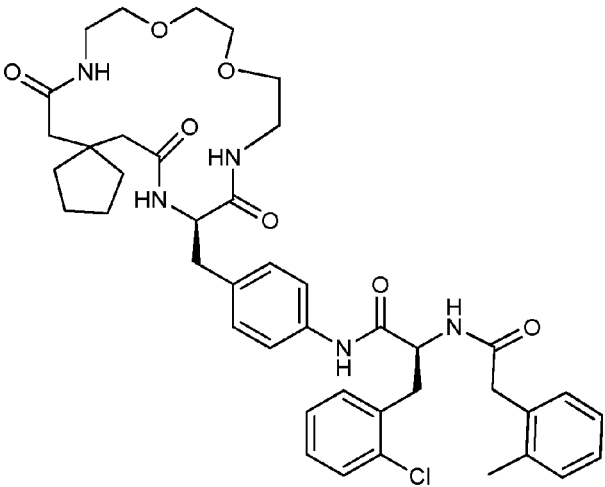
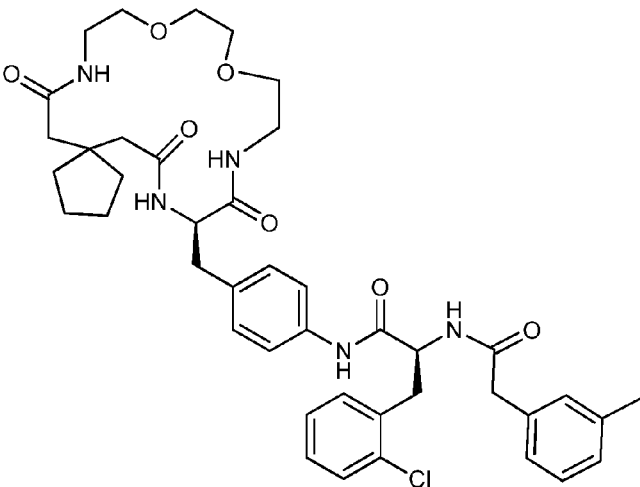
Compound No.	Structure
495	 <p>Chemical structure of Compound 495. It features a macrocyclic ring system with two ether linkages and a cyclopentyl group. The macrocycle is connected via an amide bond to a side chain. This side chain includes a benzyl group, a 2-chlorophenyl group, and a 4-methylphenyl group, all linked by amide bonds.</p>
496	 <p>Chemical structure of Compound 496. It is similar to Compound 495, but the side chain is modified. Instead of a 4-methylphenyl group, it features a 4-methylbenzyl group, which is a benzyl ring with a methyl group at the para position.</p>

FIG. 12-182

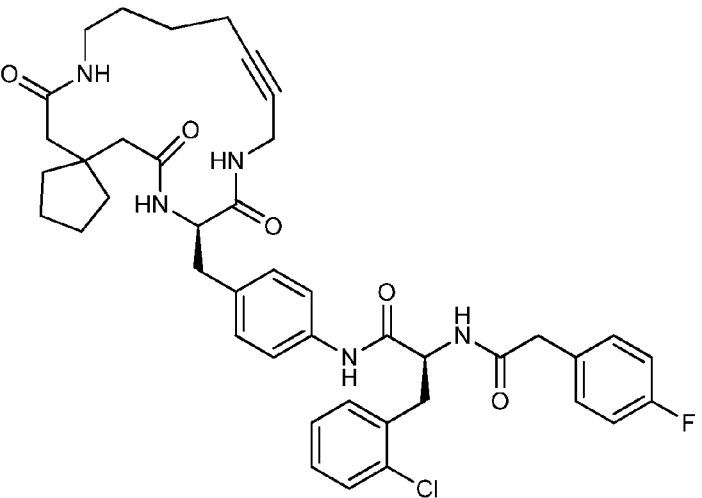
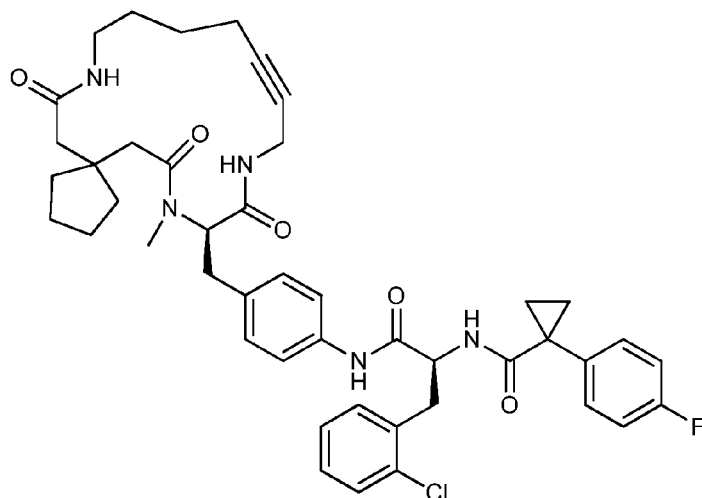
Compound No.	Structure
497	 <p>Chemical structure of Compound 497: A complex molecule featuring a cyclopentyl ring connected to a chain containing a long alkyne, a carbonyl group, and a secondary amine. This chain is further connected to a benzamide moiety, which is linked to a 2-chlorophenyl group. The structure also includes a 4-fluorophenyl group and a carbonyl group.</p>
498	 <p>Chemical structure of Compound 498: A complex molecule featuring a cyclopentyl ring connected to a chain containing a long alkyne, a carbonyl group, and a secondary amine. This chain is further connected to a benzamide moiety, which is linked to a 2-chlorophenyl group. The structure also includes a 4-fluorophenyl group and a carbonyl group.</p>

FIG. 12-183

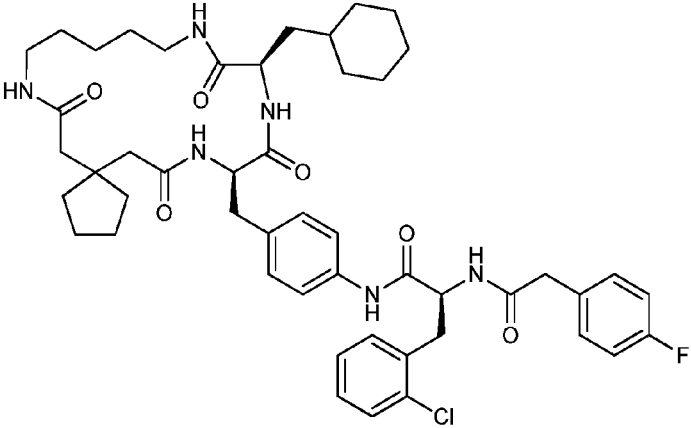
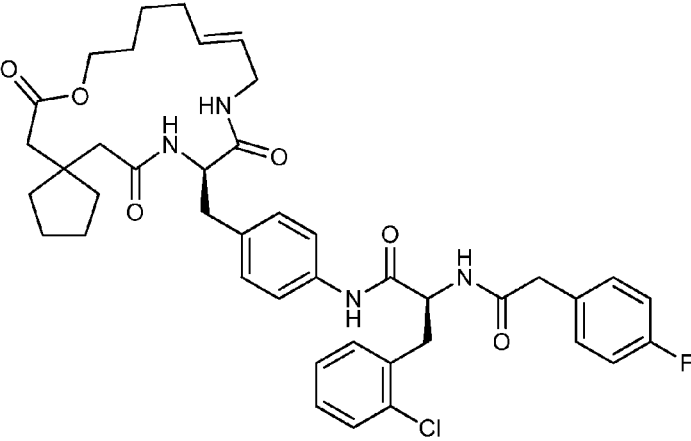
Compound No.	Structure
499	 <p>Chemical structure of Compound 499: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a chain with an amide group (HN-C=O) and a long alkyl chain ending in another amide group (NH-C=O). The right side features a 4-fluorophenyl group connected to a chain with an amide group (NH-C=O) and a 3-chlorophenyl ring. The central amide group is connected to a cyclohexyl ring.</p>
500	 <p>Chemical structure of Compound 500: A complex molecule featuring a central amide linkage. The left side includes a cyclopentyl ring connected to a chain with an amide group (HN-C=O) and a long alkyl chain ending in another amide group (NH-C=O). The right side features a 4-fluorophenyl group connected to a chain with an amide group (NH-C=O) and a 3-chlorophenyl ring. The central amide group is connected to a cyclohexyl ring.</p>

FIG. 12-184

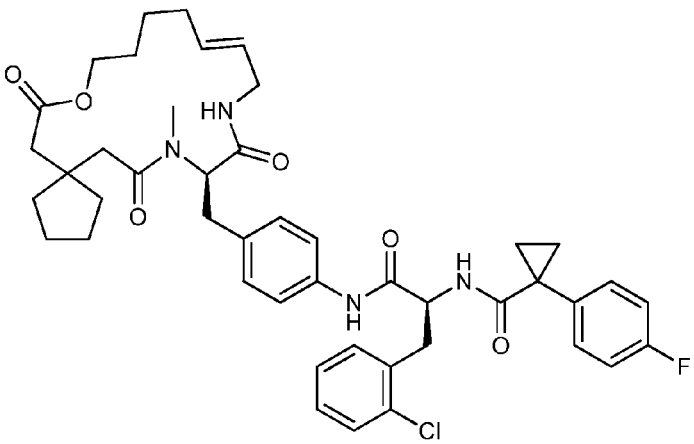
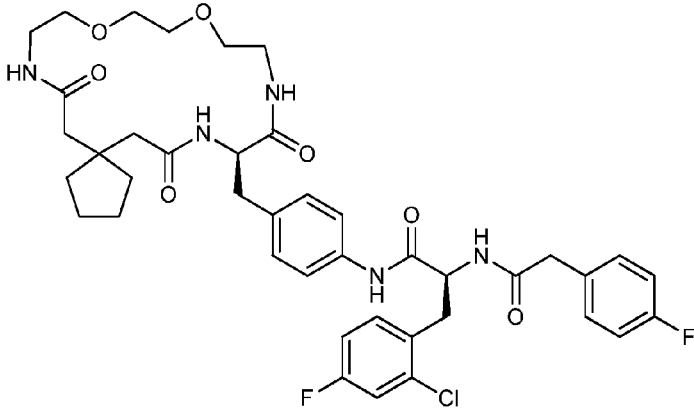
Compound No.	Structure
501	 <p>Chemical structure of Compound 501: A complex molecule featuring a cyclopentyl ring connected to a carbonyl group, which is linked to a nitrogen atom. This nitrogen is part of a larger ring system containing an amide bond and a double bond. The structure also includes a phenyl ring, a carbonyl group, and a fluorophenyl group.</p>
502	 <p>Chemical structure of Compound 502: A complex molecule featuring a cyclopentyl ring connected to a carbonyl group, which is linked to a nitrogen atom. This nitrogen is part of a larger ring system containing an amide bond and a double bond. The structure also includes a phenyl ring, a carbonyl group, and a fluorophenyl group.</p>

FIG. 12-185

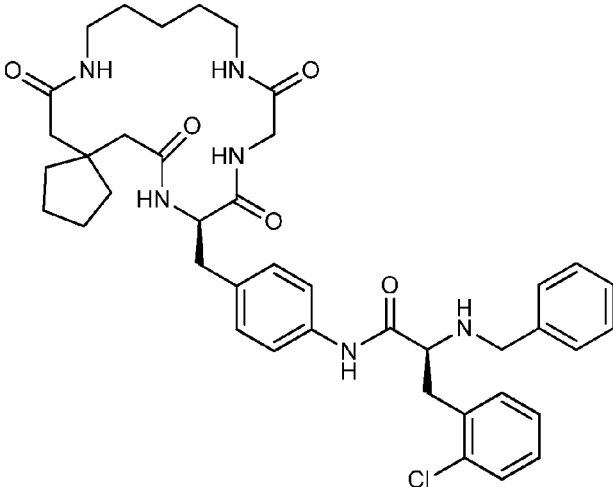
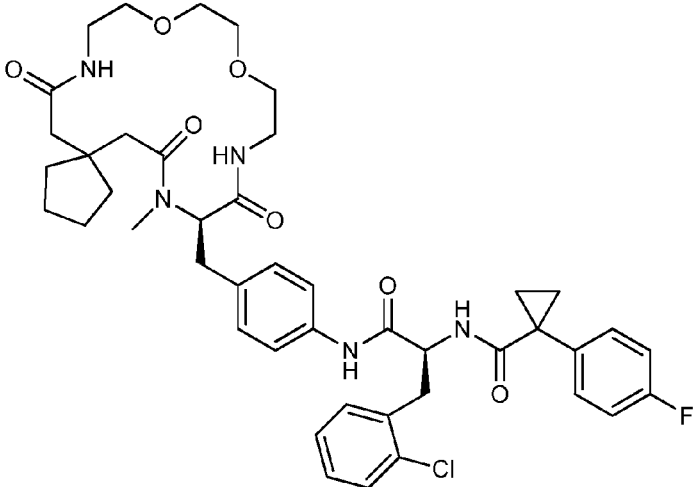
Compound No.	Structure
503	 <p>Chemical structure of Compound 503: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a benzyl group and a 4-chlorobenzyl group.</p>
504	 <p>Chemical structure of Compound 504: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This system is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a 3-chlorobenzyl group and a 4-fluorophenyl group.</p>

FIG. 12-186

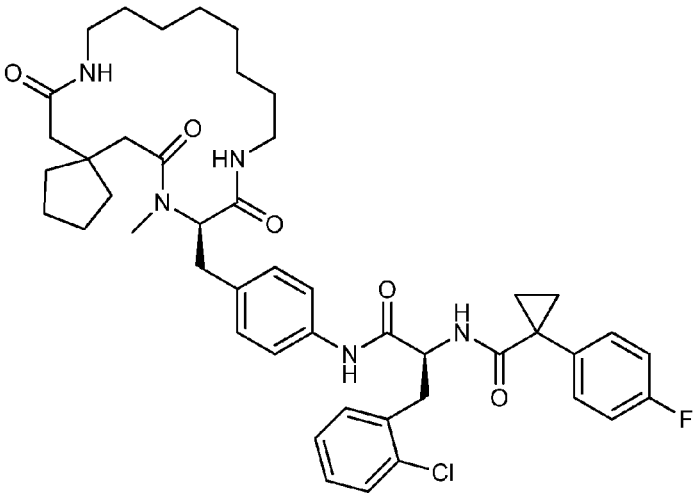
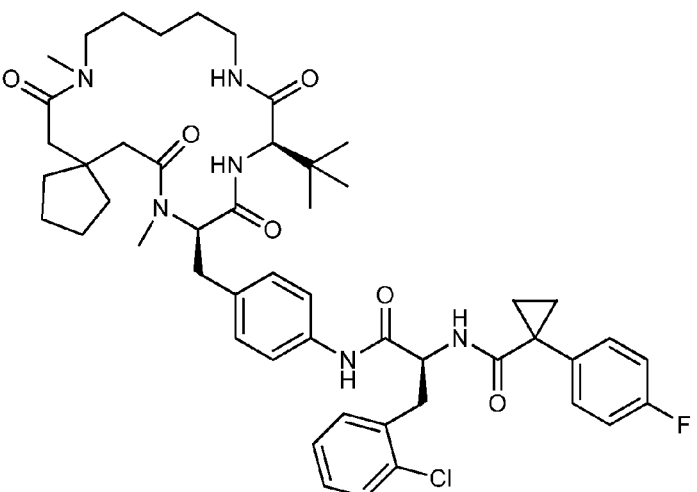
Compound No.	Structure
505	 <p>Chemical structure of Compound 505. It features a macrocyclic amide ring (10-membered) with a cyclopentyl group attached to one of the amide nitrogens. A side chain is attached to the macrocycle via a chiral center (indicated by a wedge bond). This side chain includes a benzamide moiety, a 2-chlorophenyl group, and a 4-fluorophenyl group connected via a cyclopropane ring.</p>
506	 <p>Chemical structure of Compound 506. It is similar to Compound 505, but the side chain is modified. The macrocyclic amide ring is substituted with a methyl group on one nitrogen and a tert-butyl group on the other. The side chain remains the same as in Compound 505, featuring a benzamide moiety, a 2-chlorophenyl group, and a 4-fluorophenyl group connected via a cyclopropane ring.</p>

FIG. 12-187

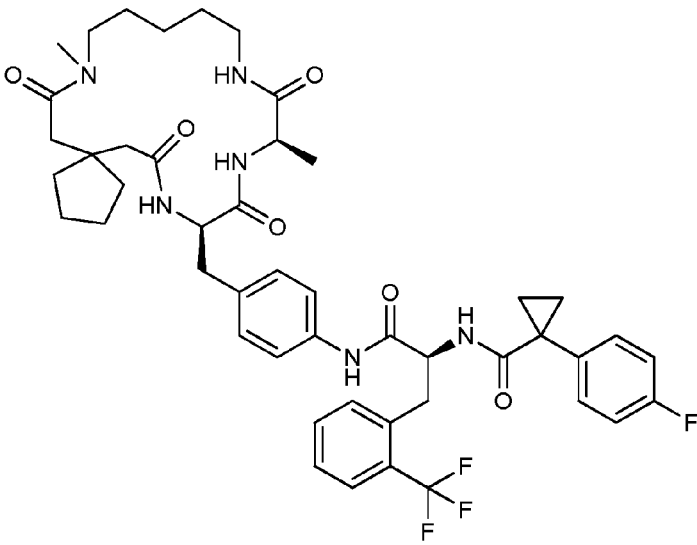
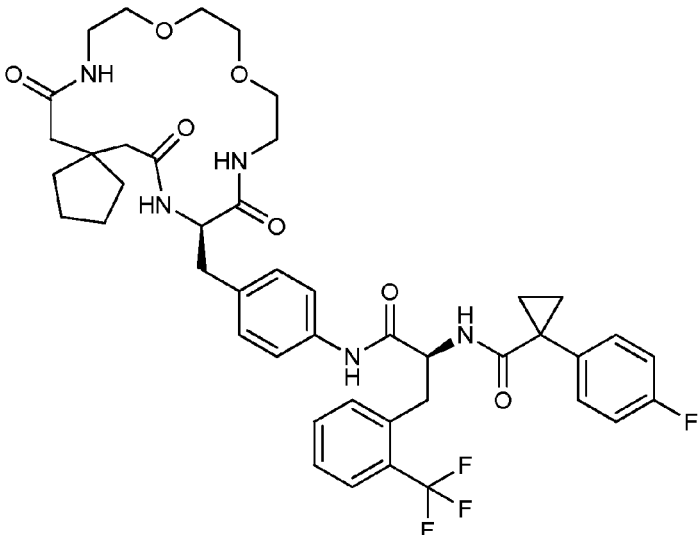
Compound No.	Structure
507	 <p>Chemical structure of Compound 507. It features a 10-membered cyclic urea ring with a methyl group on the nitrogen and a cyclopentyl ring fused to the ring. A side chain is attached to the ring, consisting of a chiral center (wedge bond) connected to a benzyl group, which is further connected to a benzamide group. This benzamide is linked to a chiral center (dash bond) connected to a carbonyl group, which is further connected to a cyclopropyl group and a 4-fluorophenyl group. A trifluoromethyl group is attached to the benzamide ring.</p>
508	 <p>Chemical structure of Compound 508. It features a 10-membered cyclic urea ring with a methyl group on the nitrogen and a cyclopentyl ring fused to the ring. A side chain is attached to the ring, consisting of a chiral center (wedge bond) connected to a benzyl group, which is further connected to a benzamide group. This benzamide is linked to a chiral center (dash bond) connected to a carbonyl group, which is further connected to a cyclopropyl group and a 4-fluorophenyl group. A trifluoromethyl group is attached to the benzamide ring.</p>

FIG. 12-188

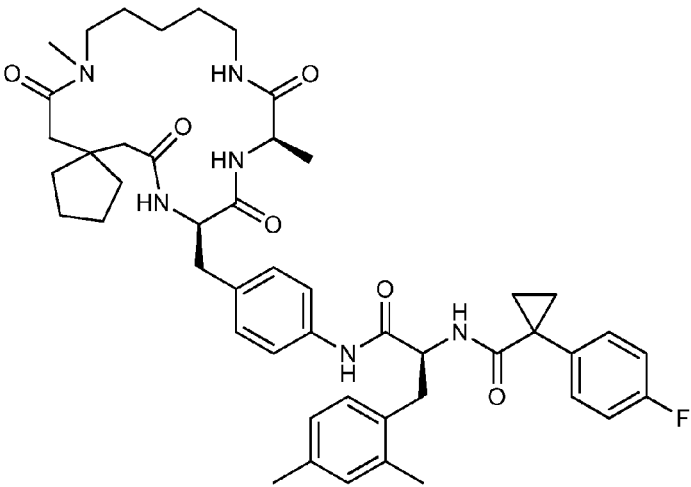
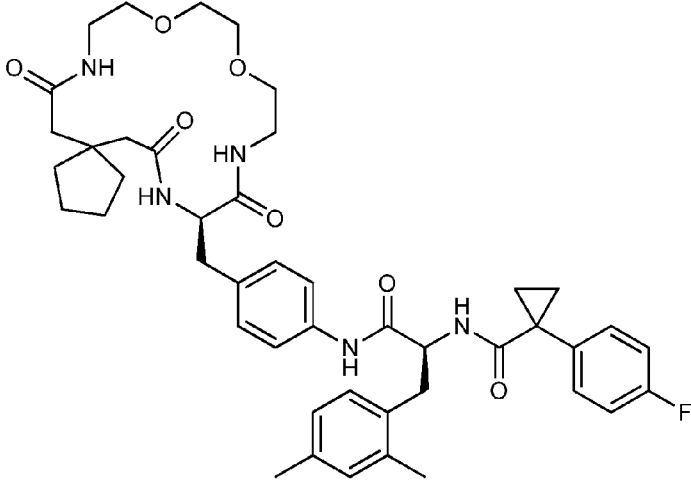
Compound No.	Structure
509	 <p>Chemical structure of Compound 509: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a cyclopentyl group and a side chain containing a benzamide moiety. The benzamide is further substituted with a 4-fluorophenyl group and a 3,5-dimethylphenyl group. The side chain also includes a carbonyl group and a methylene group.</p>
510	 <p>Chemical structure of Compound 510: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a cyclopentyl group and a side chain containing a benzamide moiety. The benzamide is further substituted with a 4-fluorophenyl group and a 3,5-dimethylphenyl group. The side chain also includes a carbonyl group and a methylene group.</p>

FIG. 12-189

Compound No.	Structure
511	
512	

FIG. 12-190

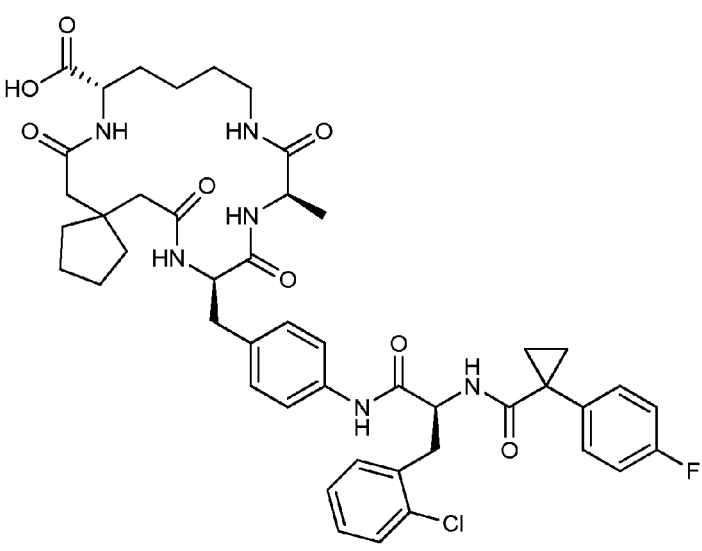
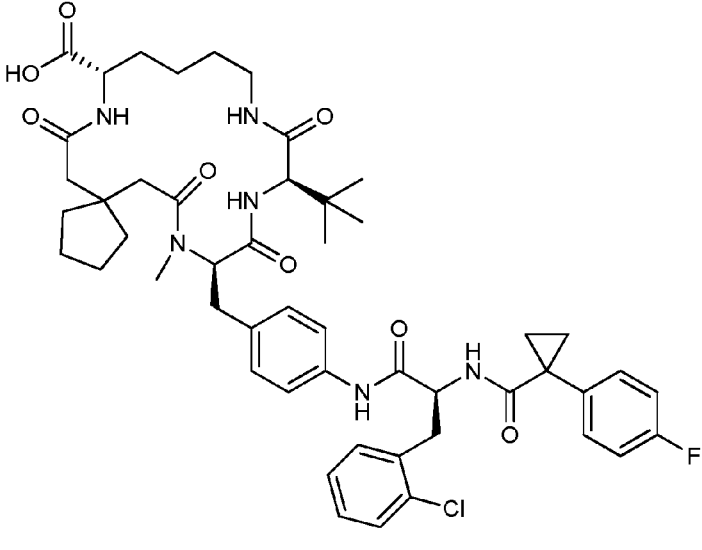
Compound No.	Structure
513	 <p>Chemical structure of Compound 513. It features a macrocyclic core with a carboxylic acid group (HO-C(=O)-) and a cyclopentyl ring. The structure includes a side chain with a benzyl group, a 2-chlorophenyl group, and a 4-fluorophenyl group. The side chain is connected to the macrocycle via an amide linkage.</p>
514	 <p>Chemical structure of Compound 514. It features a macrocyclic core with a carboxylic acid group (HO-C(=O)-) and a cyclopentyl ring. The structure includes a side chain with a benzyl group, a 2-chlorophenyl group, and a 4-fluorophenyl group. The side chain is connected to the macrocycle via an amide linkage, and the macrocycle also contains a methyl group.</p>

FIG. 12-191

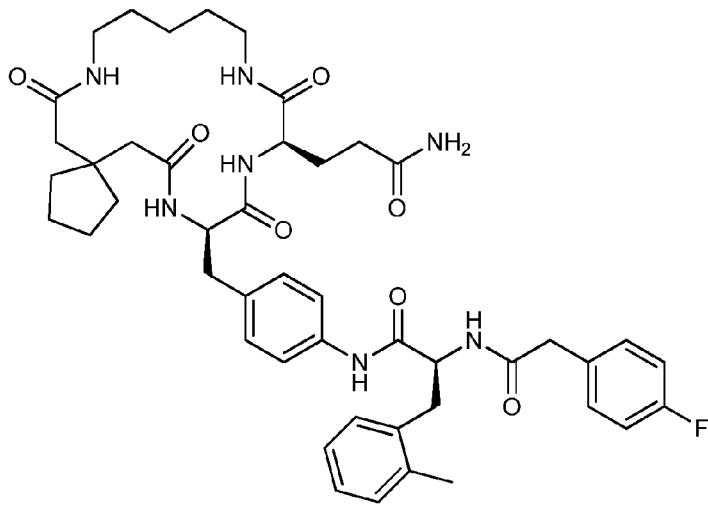
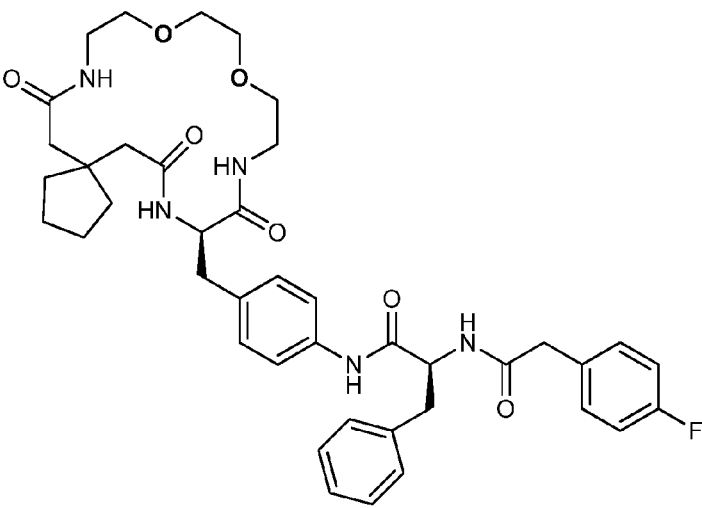
Compound No.	Structure
515	 <p>Chemical structure of Compound 515: A complex molecule featuring a cyclopentane ring substituted with a 1,4-bis(amide)hexyl chain. This chain is further substituted with a 2-((4-((4-aminobutyl)amino)-2-oxoethyl)phenyl)ethylamino group. The amine is part of a 2-((4-((4-((4-aminobutyl)amino)-2-oxoethyl)phenyl)ethyl)amino)-2-oxoethyl)phenyl group, which is linked to a 4-fluorophenyl group via an amide bond.</p>
516	 <p>Chemical structure of Compound 516: A complex molecule featuring a cyclopentane ring substituted with a 1,4-bis(amide)hexyl chain. This chain is further substituted with a 2-((4-((4-((4-aminobutyl)amino)-2-oxoethyl)phenyl)ethyl)amino)-2-oxoethyl)phenyl group, which is linked to a 4-fluorophenyl group via an amide bond. The structure is similar to Compound 515 but with a different amine linkage.</p>

FIG. 12-192

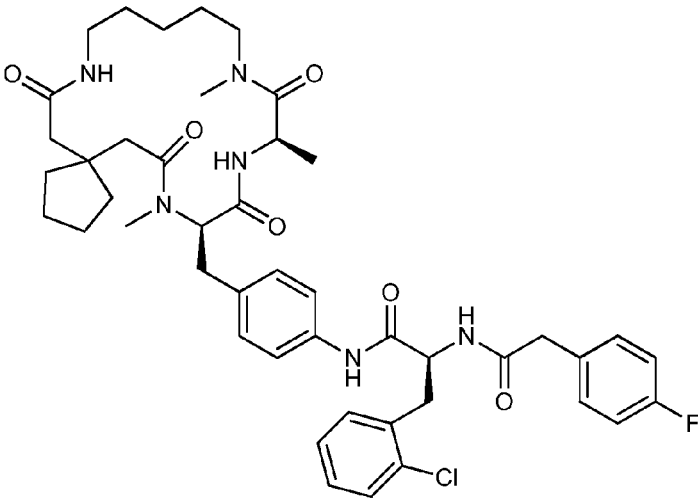
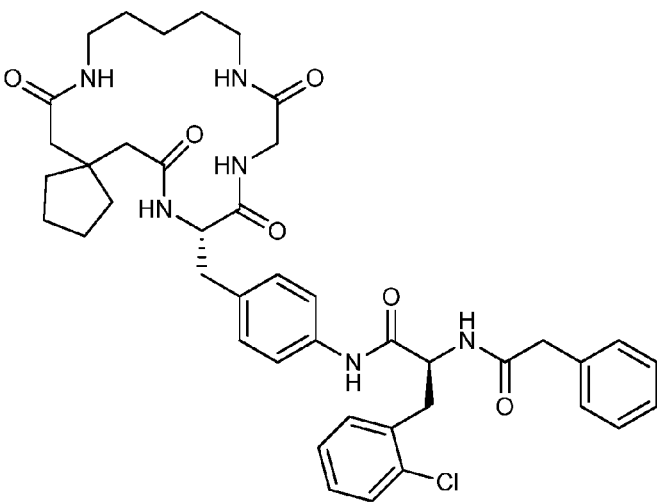
Compound No.	Structure
518	 <p>Chemical structure of Compound 518. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzamide moiety. The benzamide is further linked to a chiral center that is part of a side chain containing a 2-chlorophenyl group and a 4-fluorophenyl group.</p>
519	 <p>Chemical structure of Compound 519. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups). This system is linked via a chiral center to a benzamide moiety. The benzamide is further linked to a chiral center that is part of a side chain containing a 2-chlorophenyl group and a phenyl group.</p>

FIG. 12-193

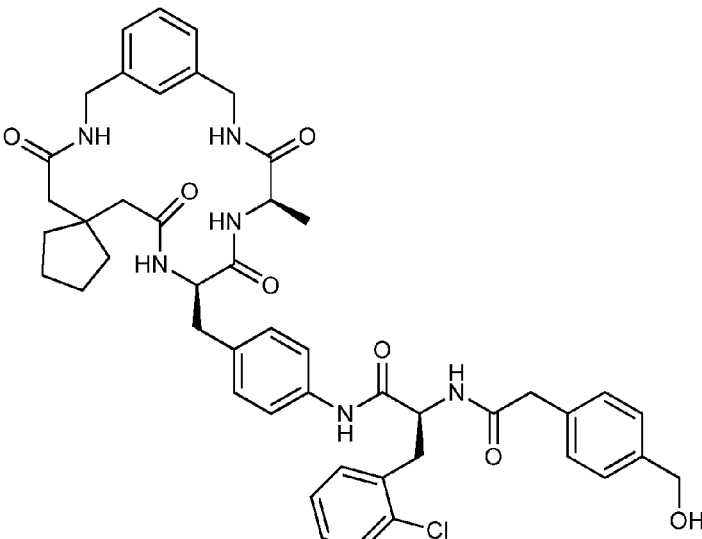
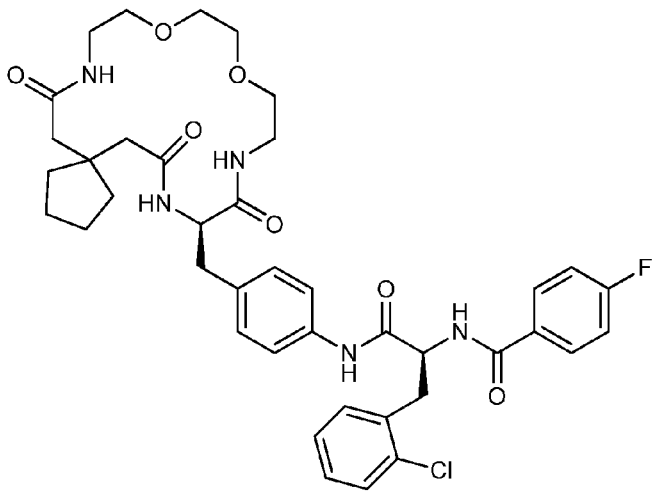
Compound No.	Structure
520	 <p>Chemical structure of Compound 520: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C(=O)-CH₂-) and a side chain containing multiple amide linkages. The side chain includes a benzyl group, a 4-hydroxybenzyl group, and a 2-chlorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>
521	 <p>Chemical structure of Compound 521: A complex molecule featuring a cyclopentane ring substituted with a carboxamide group (NH-C(=O)-CH₂-) and a side chain containing multiple amide linkages. The side chain includes a benzyl group, a 4-fluorobenzyl group, and a 2-chlorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-194

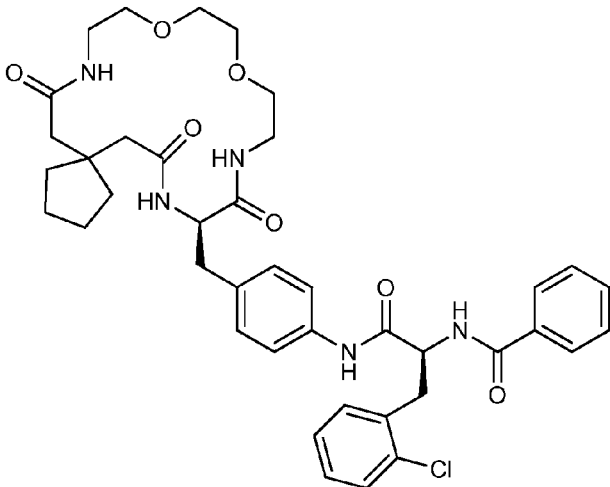
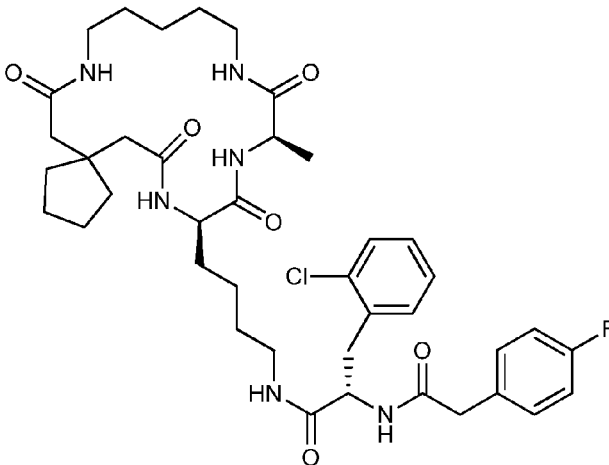
Compound No.	Structure
522	 <p>Chemical structure of Compound 522: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered amide ring). This system is linked via an amide bond to a side chain containing a benzene ring, a carbonyl group, and a chiral center. The side chain also includes a benzamide moiety and a 2-chlorophenyl group.</p>
523	 <p>Chemical structure of Compound 523: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered amide ring). This system is linked via an amide bond to a side chain containing a benzene ring, a carbonyl group, and a chiral center. The side chain also includes a benzamide moiety and a 2-chlorophenyl group.</p>

FIG. 12-195

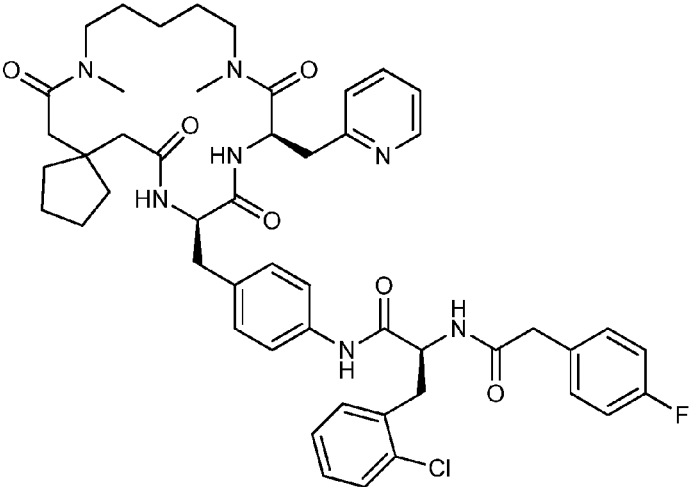
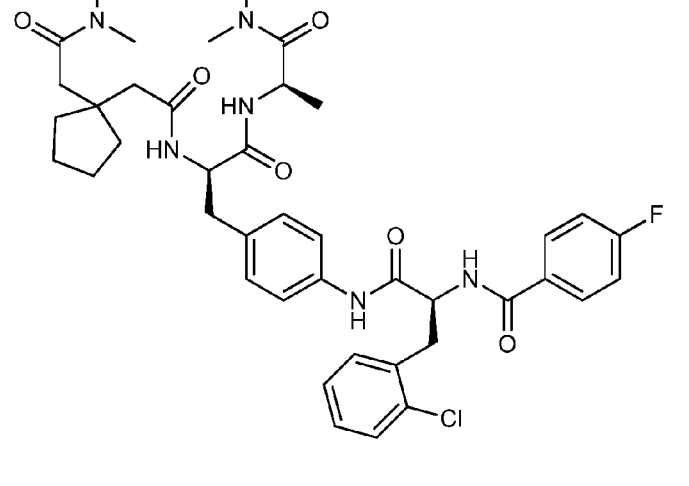
Compound No.	Structure
524	 <p>Chemical structure of Compound 524. The molecule features a 1,4-bis(methyl)-1,4-diazepane-2,7-dione core. One nitrogen is substituted with a 2-(cyclopentylmethyl)ethyl group, and the other with a 2-(pyridin-2-ylmethyl)ethyl group. The pyridine ring is attached via its 2-position. The 2-position of the pyridine ring is also substituted with a 2-(2-chlorophenyl)-N-(4-(4-fluorophenyl)-2-oxoethyl)-L-propanamide side chain. The side chain is attached to the 2-position of the pyridine ring via its 2-position. The side chain consists of a 2-chlorophenyl group attached to a 2-oxoethyl group, which is further attached to an L-propanamide moiety. The L-propanamide moiety is attached to the 2-position of the pyridine ring via its 2-position.</p>
525	 <p>Chemical structure of Compound 525. The molecule features a 1,4-bis(methyl)-1,4-diazepane-2,7-dione core. One nitrogen is substituted with a 2-(cyclopentylmethyl)ethyl group, and the other with a 2-(pyridin-2-ylmethyl)ethyl group. The pyridine ring is attached via its 2-position. The 2-position of the pyridine ring is also substituted with a 2-(2-chlorophenyl)-N-(4-(4-fluorophenyl)-2-oxoethyl)-L-propanamide side chain. The side chain is attached to the 2-position of the pyridine ring via its 2-position. The side chain consists of a 2-chlorophenyl group attached to a 2-oxoethyl group, which is further attached to an L-propanamide moiety. The L-propanamide moiety is attached to the 2-position of the pyridine ring via its 2-position.</p>

FIG. 12-196

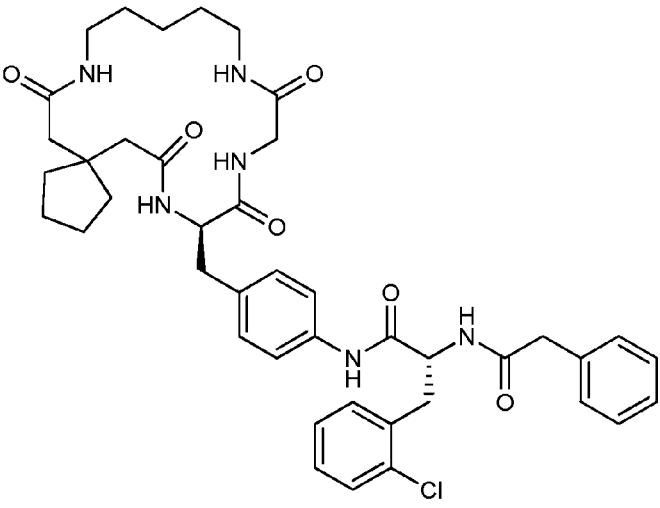
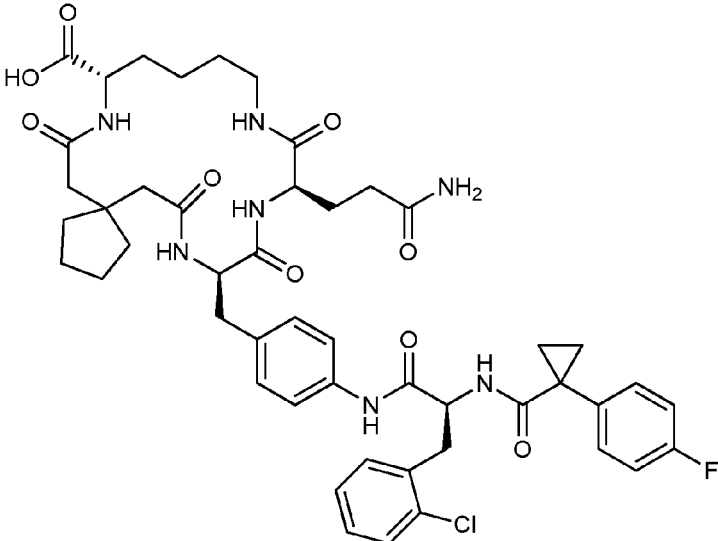
Compound No.	Structure
526	 <p>Chemical structure of Compound 526: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a 3-chlorophenyl group and a benzyl group. The benzyl group is part of a side chain ending in a benzamide group.</p>
527	 <p>Chemical structure of Compound 527: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a 3-chlorophenyl group and a benzyl group. The benzyl group is part of a side chain ending in a benzamide group. The molecule also includes a carboxylic acid group and a primary amide group.</p>

FIG. 12-197

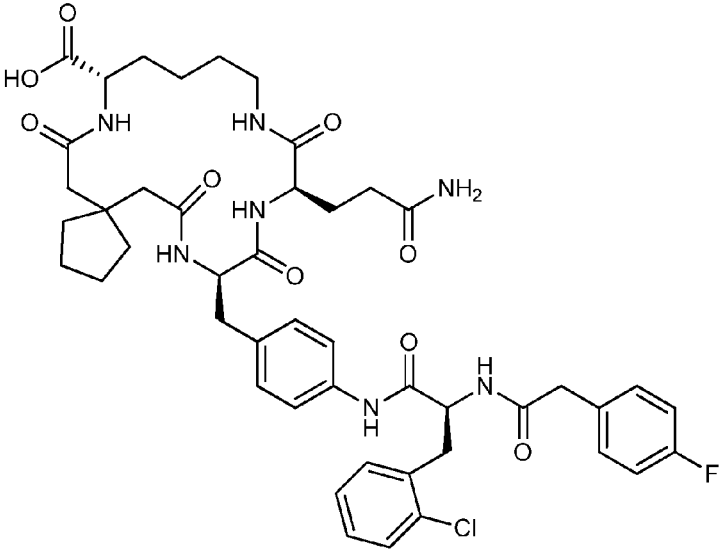
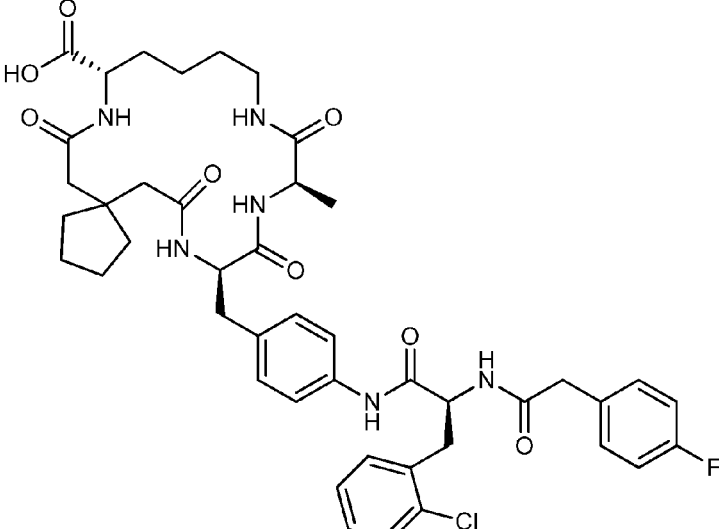
Compound No.	Structure
528	 <p>Chemical structure of Compound 528. It features a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and a side chain containing multiple amide bonds. The side chain includes a 4-aminobutyl group, a 2-chlorophenyl group, and a 4-fluorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>
529	 <p>Chemical structure of Compound 529. It is similar to Compound 528 but lacks the 4-aminobutyl group. The side chain includes a 2-chlorophenyl group and a 4-fluorophenyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-198

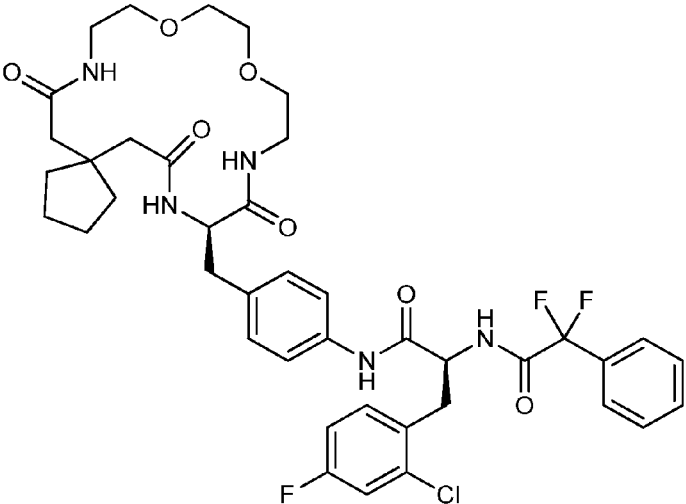
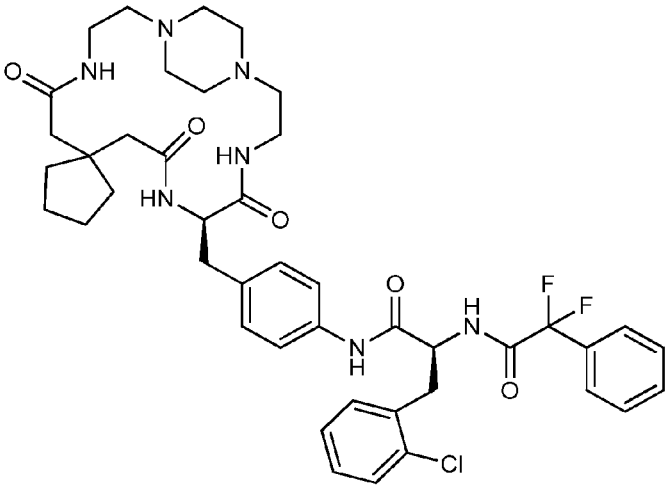
Compound No.	Structure
530	 <p>Chemical structure of Compound 530. The molecule features a 1,3-dioxane ring system fused to a cyclopentane ring. This is connected via an amide linkage to a chiral center (marked with a wedge bond) which is further connected to a benzene ring. The benzene ring is linked to another amide group, which is connected to a chiral center (marked with a wedge bond) that is linked to a benzene ring with a chlorine and a fluorine substituent. The final part of the molecule is a benzamide group with a trifluoromethyl substituent.</p>
531	 <p>Chemical structure of Compound 531. The molecule features a 1,3-diazepane ring system fused to a cyclopentane ring. This is connected via an amide linkage to a chiral center (marked with a wedge bond) which is further connected to a benzene ring. The benzene ring is linked to another amide group, which is connected to a chiral center (marked with a wedge bond) that is linked to a benzene ring with a chlorine and a fluorine substituent. The final part of the molecule is a benzamide group with a trifluoromethyl substituent.</p>

FIG. 12-199

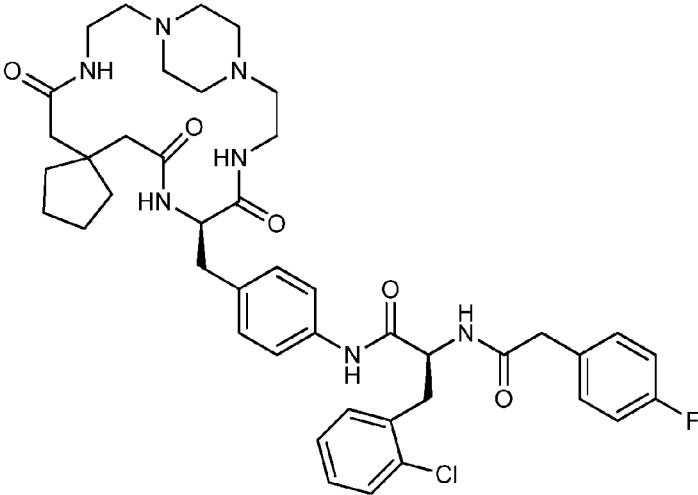
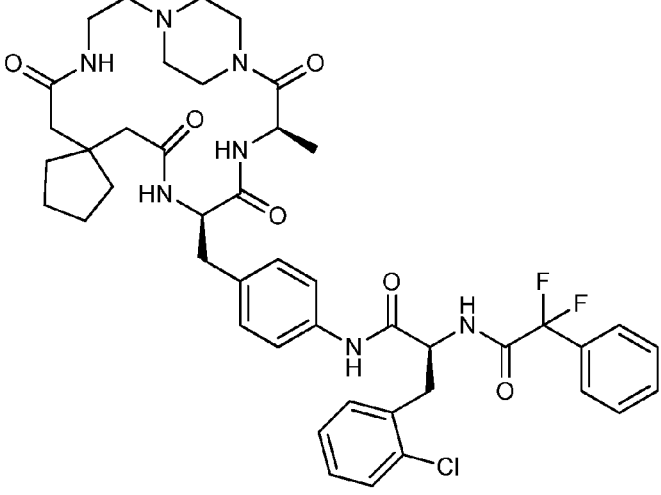
Compound No.	Structure
532	 <p>Chemical structure of Compound 532: A complex molecule featuring a 1,4-bis(morpholin-4-yl)butane-1,4-dione core. One morpholine ring is substituted with a cyclopentylmethyl group. The other morpholine ring is substituted with a 1-((2-chlorophenyl)methyl)-4-((4-(4-fluorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl)amino)butan-1-yl group.</p>
533	 <p>Chemical structure of Compound 533: A complex molecule featuring a 1,4-bis(morpholin-4-yl)butane-1,4-dione core. One morpholine ring is substituted with a cyclopentylmethyl group. The other morpholine ring is substituted with a 1-((2-chlorophenyl)methyl)-4-((4-(2,2-difluorobenzoylamino)-2-methylbutan-1-yl)amino)butan-1-yl group.</p>

FIG. 12-200

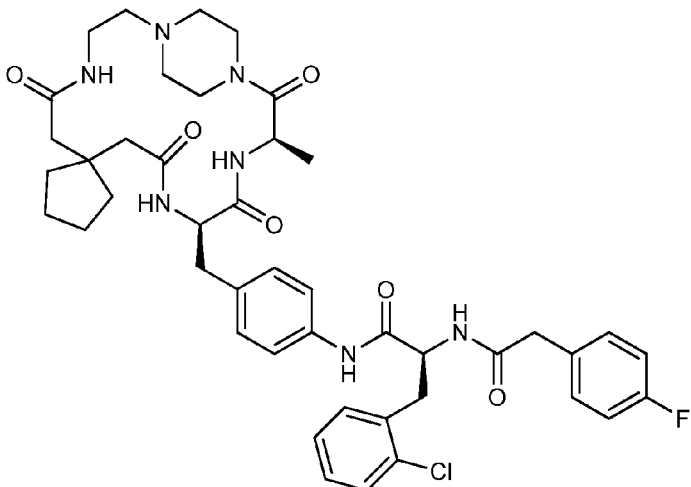
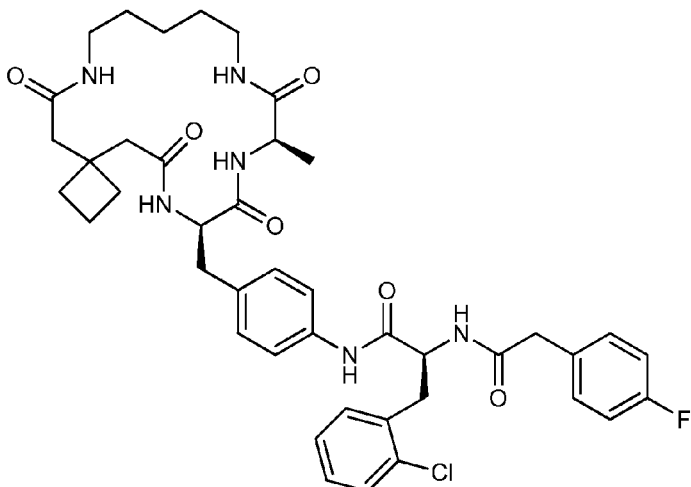
Compound No.	Structure
534	 <p>Chemical structure of compound 534. It features a 1,4-bis(methylamino)butane moiety linked to a cyclopentyl ring via a carbonyl group. This cyclopentyl ring is further connected to a chiral center (marked with a wedge bond) which is part of a chain containing a benzamide group, a 2-chlorophenyl group, and a 4-fluorophenyl group.</p>
535	 <p>Chemical structure of compound 535. It is similar to compound 534, but the 1,4-bis(methylamino)butane moiety is replaced by a 1,4-bis(methylamino)hexane moiety. The rest of the structure, including the cyclobutyl ring and the chiral center with the benzamide, 2-chlorophenyl, and 4-fluorophenyl groups, remains the same.</p>

FIG. 12-201

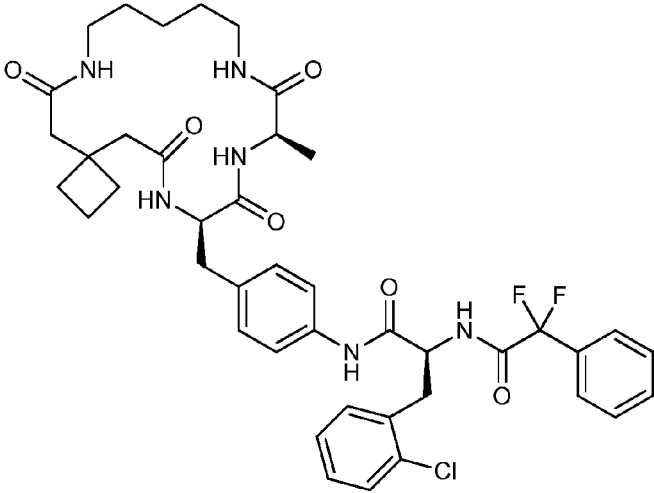
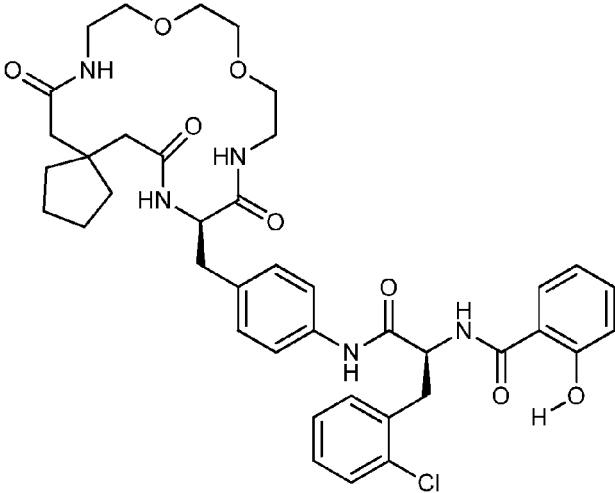
Compound No.	Structure
536	 <p>Chemical structure of Compound 536: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a cyclobutyl group and a side chain containing a chiral center (marked with a wedge bond). This side chain is further substituted with a benzyl group, which is linked to a 2-chlorophenyl ring. The 2-chlorophenyl ring is connected to a chiral center (marked with a wedge bond) that is part of a side chain ending in a 2,2-difluorophenyl group.</p>
537	 <p>Chemical structure of Compound 537: A complex molecule featuring a macrocyclic amide ring system. The macrocycle is substituted with a cyclopentyl group and a side chain containing a chiral center (marked with a wedge bond). This side chain is further substituted with a benzyl group, which is linked to a 2-chlorophenyl ring. The 2-chlorophenyl ring is connected to a chiral center (marked with a wedge bond) that is part of a side chain ending in a 2-hydroxyphenyl group.</p>

FIG. 12-202

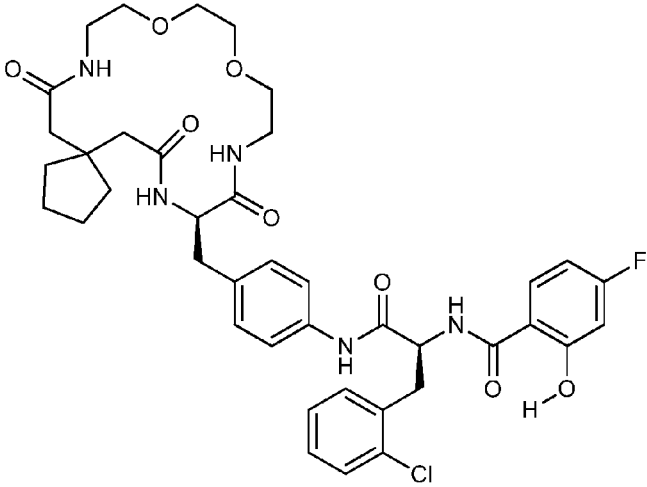
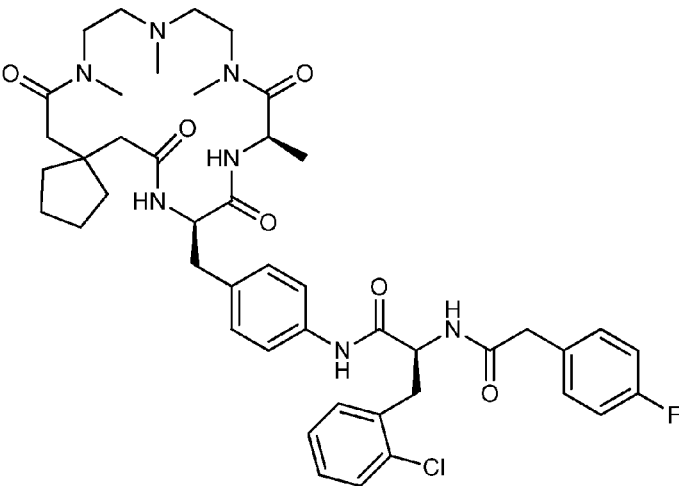
Compound No.	Structure
538	 <p>Chemical structure of Compound 538. It features a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group) connected via a linker to a benzamide moiety. The benzamide is further substituted with a 2-chlorophenyl group and a 4-fluorophenyl group. The structure includes a complex amide linkage and a fluorine atom on the phenyl ring.</p>
539	 <p>Chemical structure of Compound 539. It features a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group) connected via a linker to a benzamide moiety. The benzamide is further substituted with a 2-chlorophenyl group and a 4-fluorophenyl group. The structure includes a complex amide linkage and a fluorine atom on the phenyl ring.</p>

FIG. 12-203

[illegible]

FIG. 12-204

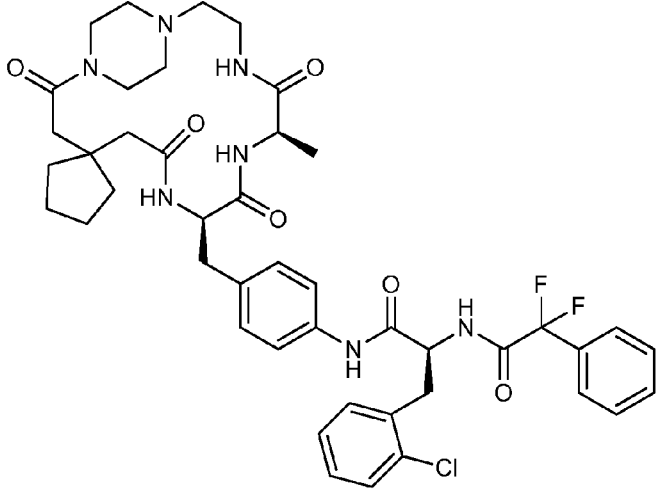
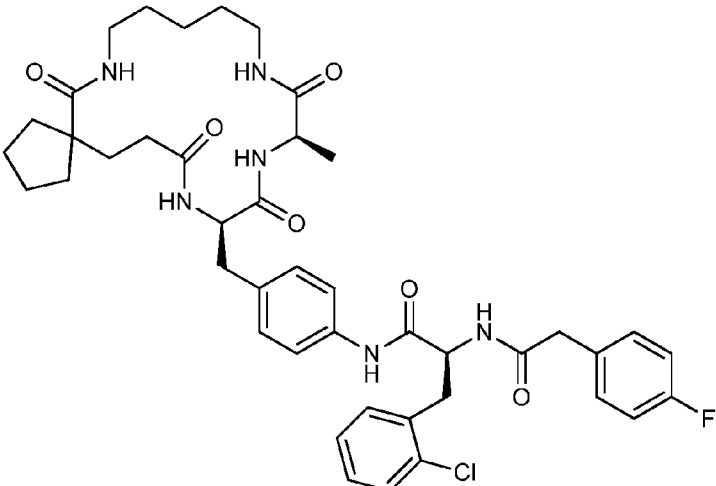
Compound No.	Structure
542	 <p>Chemical structure of Compound 542: A complex molecule featuring a piperidine ring connected via a carbonyl group to a cyclopentyl ring. This cyclopentyl ring is further connected to a chain of amide bonds. The chain includes a chiral center (marked with a wedge bond) and a 4-chlorophenyl group. The chain terminates in a 2,2-difluoro-1-phenylethan-1-yl group.</p>
543	 <p>Chemical structure of Compound 543: A complex molecule featuring a piperidine ring connected via a carbonyl group to a cyclopentyl ring. This cyclopentyl ring is further connected to a chain of amide bonds. The chain includes a chiral center (marked with a wedge bond) and a 4-chlorophenyl group. The chain terminates in a 4-fluorophenyl group.</p>

FIG. 12-205

Compound No.	Structure
544	
545	

FIG. 12-206

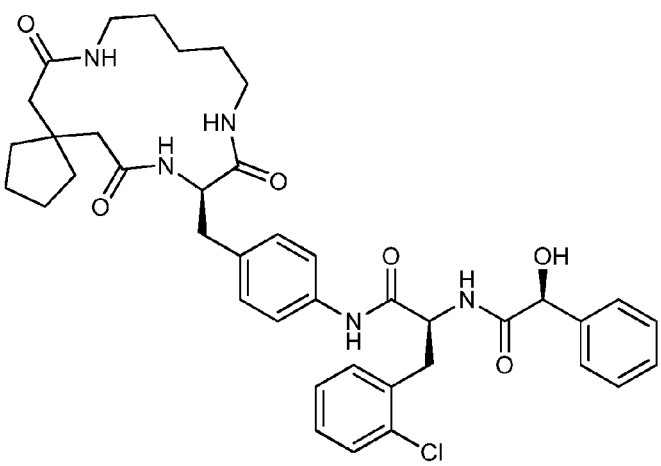
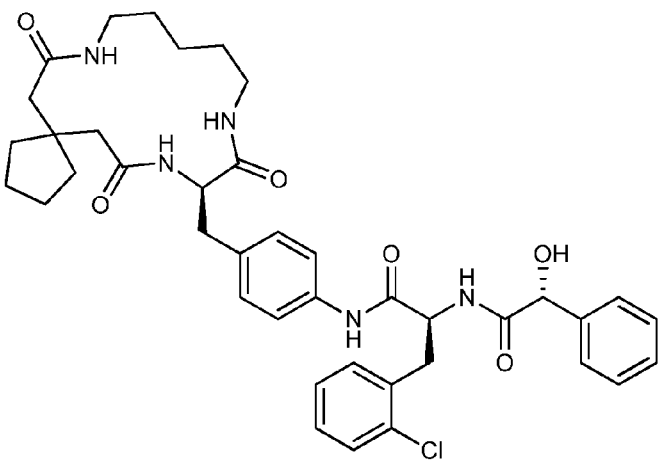
Compound No.	Structure
546	 <p>Chemical structure of Compound 546. It features a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing two amide groups) connected via a chiral center to a benzyl group. This benzyl group is further connected to a benzamide moiety, which is linked to a chiral center bearing a hydroxyl group and a benzyl group. The stereochemistry at the chiral centers is (R,R).</p>
547	 <p>Chemical structure of Compound 547. It is identical to Compound 546, but the stereochemistry at the chiral center bearing the hydroxyl group is (S), indicated by a dashed bond to the hydroxyl group.</p>

FIG. 12-207

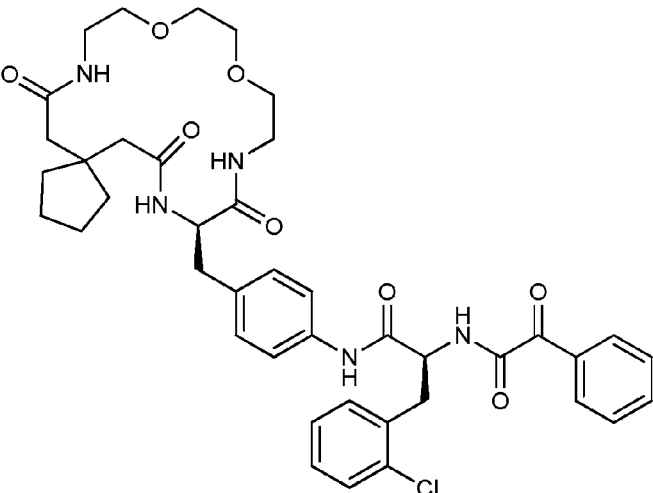
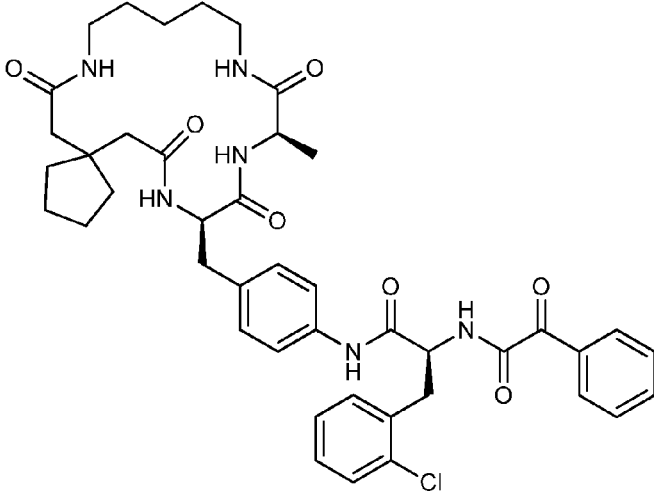
Compound No.	Structure
548	 <p>Chemical structure of Compound 548. It features a cyclopentane ring substituted with a carbonyl group and a side chain containing a carbonyl and an amide linkage. This side chain is connected to a benzene ring, which is further linked to a 2-chlorophenyl group and a benzoyl group. The structure also includes a complex ring system with multiple amide and carbonyl groups, and a long chain with an ether linkage.</p>
549	 <p>Chemical structure of Compound 549. It features a cyclopentane ring substituted with a carbonyl group and a side chain containing a carbonyl and an amide linkage. This side chain is connected to a benzene ring, which is further linked to a 2-chlorophenyl group and a benzoyl group. The structure also includes a complex ring system with multiple amide and carbonyl groups, and a long chain with an ether linkage.</p>

FIG. 12-208

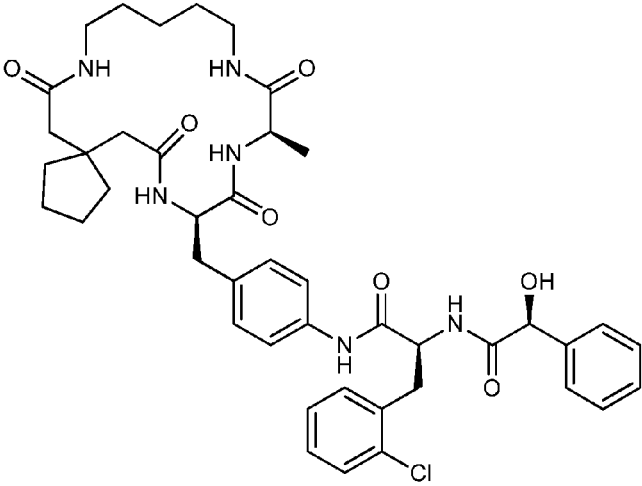
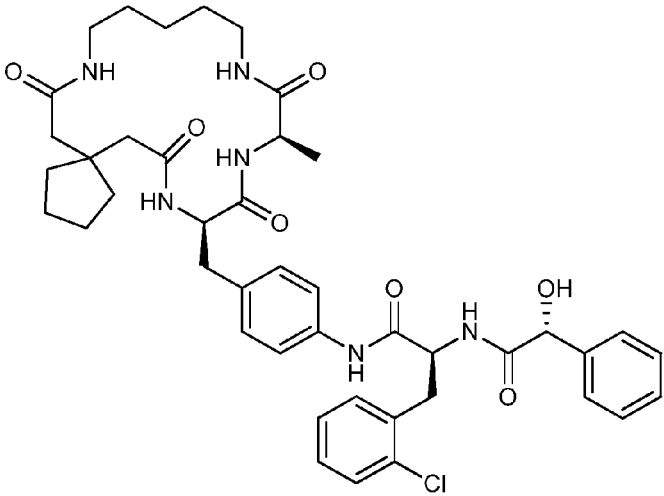
Compound No.	Structure
550	 <p>Chemical structure of Compound 550. It features a complex molecule with a cyclopentane ring fused to a piperidine ring. The piperidine ring is substituted with a long chain containing multiple amide and ester groups. The chain includes a benzamide moiety, a 2-chlorophenyl group, and a 1-phenylethanol moiety.</p>
551	 <p>Chemical structure of Compound 551. It is similar to Compound 550, but the stereochemistry of the 1-phenylethanol moiety is different, indicated by the dashed bond to the hydroxyl group.</p>

FIG. 12-209

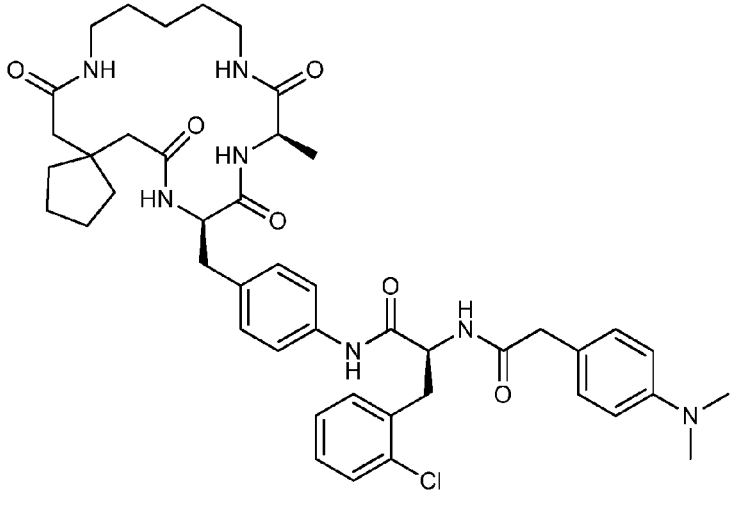
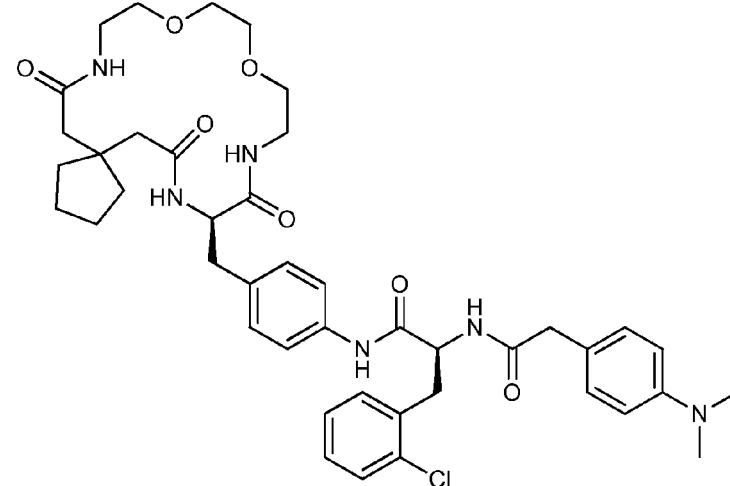
Compound No.	Structure
552	 <p>Chemical structure of compound 552. It features a bicyclic amide system (cyclopentane fused to a six-membered ring with two amide groups). This is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center linked to a benzamide moiety, and finally to a dimethylaminomethyl group.</p>
553	 <p>Chemical structure of compound 553. It is similar to compound 552, but the bicyclic amide system is replaced by a macrocyclic structure containing an ether linkage.</p>

FIG. 12-210

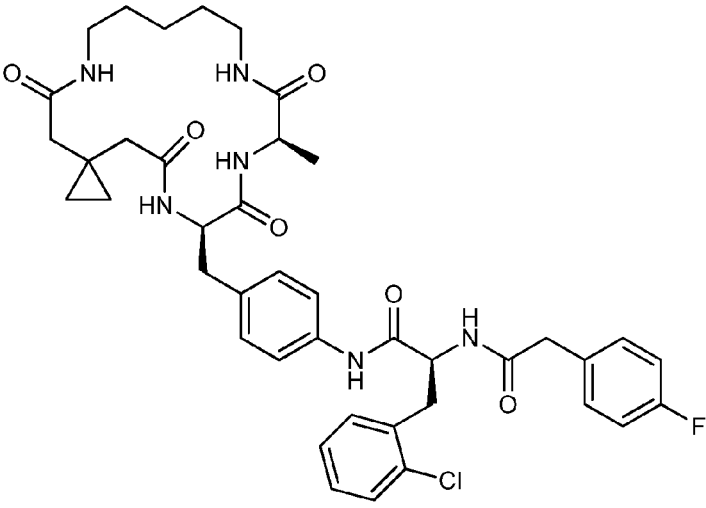
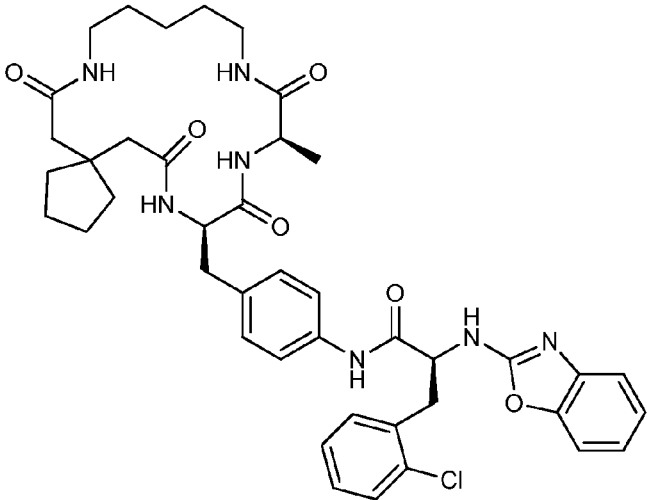
Compound No.	Structure
554	 <p>Chemical structure of Compound 554: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopropyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a side chain containing a benzyl group, a 2-chlorophenyl group, and a 4-fluorophenyl group.</p>
555	 <p>Chemical structure of Compound 555: A complex molecule featuring a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. The macrocycle is linked via an amide bond to a side chain containing a benzyl group, a 2-chlorophenyl group, and a benzoxazole group.</p>

FIG. 12-211

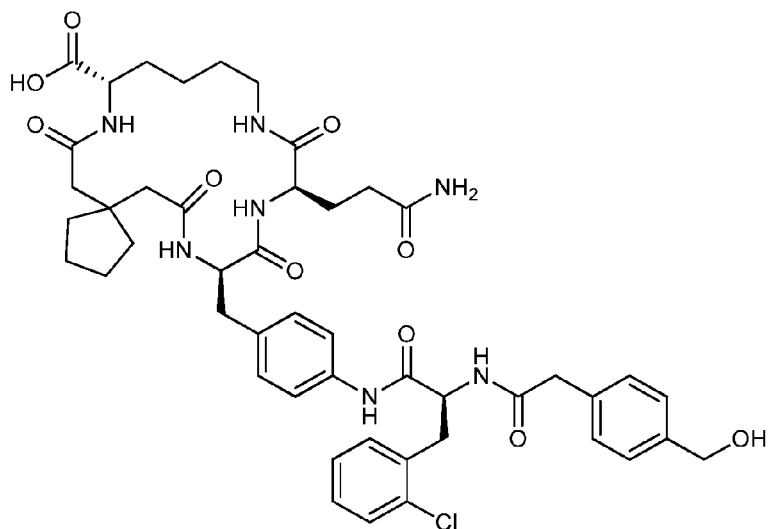
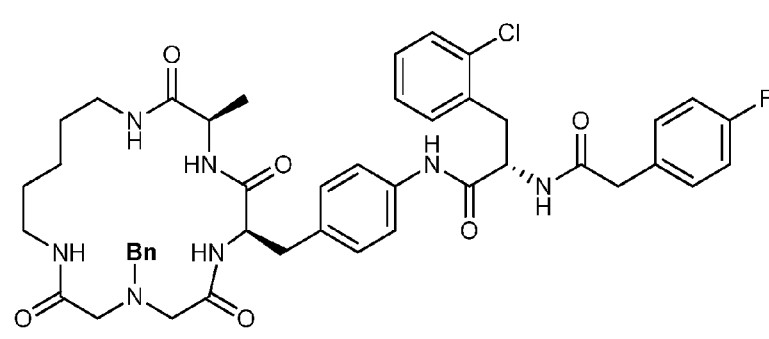
Compound No.	Structure
556	 <p>Chemical structure of Compound 556: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and an amide group (-NH-C(=O)-). This amide is part of a chain that includes a benzamide moiety (-NH-C(=O)-C₆H₅), a 2-chlorophenyl group, and a 4-hydroxybenzamide moiety (-NH-C(=O)-CH₂-C₆H₄-OH).</p>
557	 <p>Chemical structure of Compound 557: A complex molecule featuring a benzyl-protected amide (Bn-NH-C(=O)-) and a 2-chlorophenyl group. It also includes a 4-fluorobenzamide moiety (-NH-C(=O)-CH₂-C₆H₄-F).</p>

FIG. 12-212

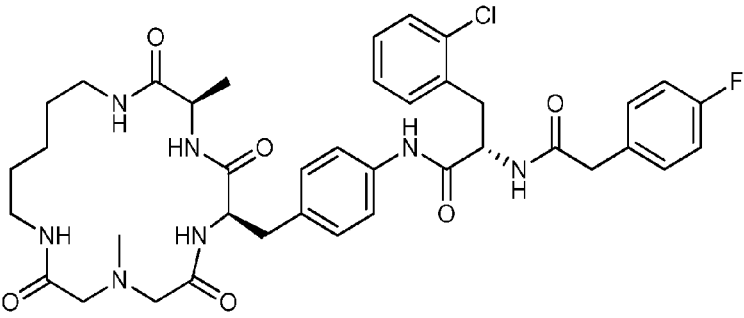
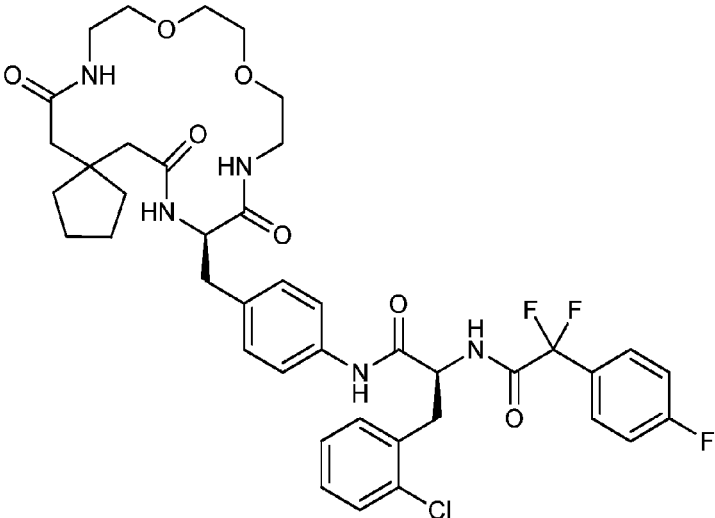
Compound No.	Structure
558	 <p>Chemical structure of Compound 558: A complex molecule featuring a central benzene ring. One side of the benzene ring is connected to a 6-membered lactam ring (piperidin-2-one) via a methylene group. The other side of the benzene ring is connected to a 6-membered lactam ring (piperidin-2-one) via a methylene group. This second lactam ring is further substituted with a 4-fluorophenyl group and a 4-chlorophenyl group. The molecule also includes a 4-fluorophenyl group and a 4-chlorophenyl group.</p>
559	 <p>Chemical structure of Compound 559: A complex molecule featuring a central benzene ring. One side of the benzene ring is connected to a 6-membered lactam ring (piperidin-2-one) via a methylene group. The other side of the benzene ring is connected to a 6-membered lactam ring (piperidin-2-one) via a methylene group. This second lactam ring is further substituted with a 4-fluorophenyl group and a 4-chlorophenyl group. The molecule also includes a 4-fluorophenyl group and a 4-chlorophenyl group.</p>

FIG. 12-213

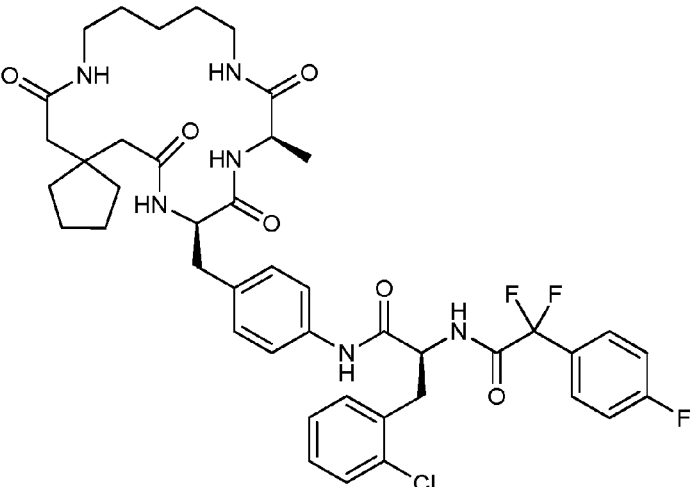
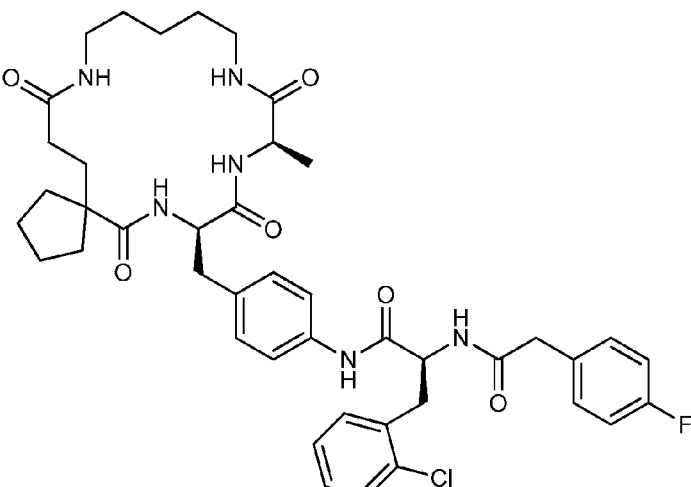
Compound No.	Structure
560	 <p>Chemical structure of Compound 560. It features a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. A side chain is attached to the macrocycle, consisting of a chiral center (with a methyl group) linked to a benzyl group, which is further linked to a 2-chlorophenyl group. The side chain also includes a 2-fluorophenyl group and a 4-fluorophenyl group.</p>
561	 <p>Chemical structure of Compound 561. It features a macrocyclic amide ring (12-membered) with a cyclopentyl group attached to one of the amide nitrogens. A side chain is attached to the macrocycle, consisting of a chiral center (with a methyl group) linked to a benzyl group, which is further linked to a 2-chlorophenyl group. The side chain also includes a 2-fluorophenyl group and a 4-fluorophenyl group.</p>

FIG. 12-214

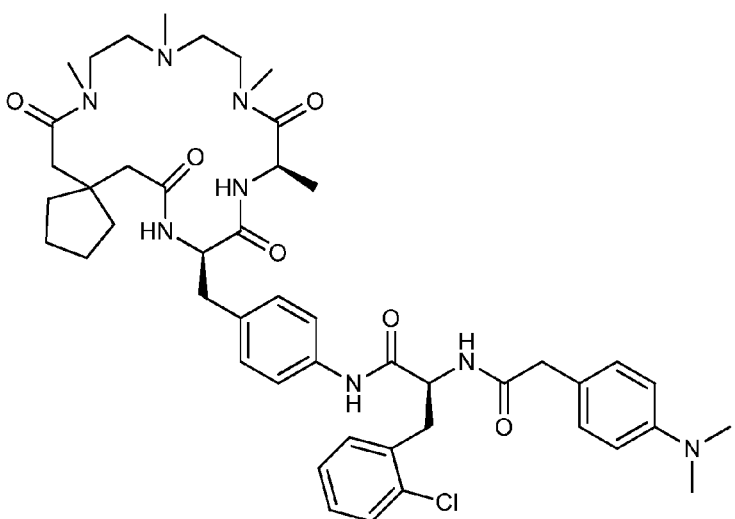
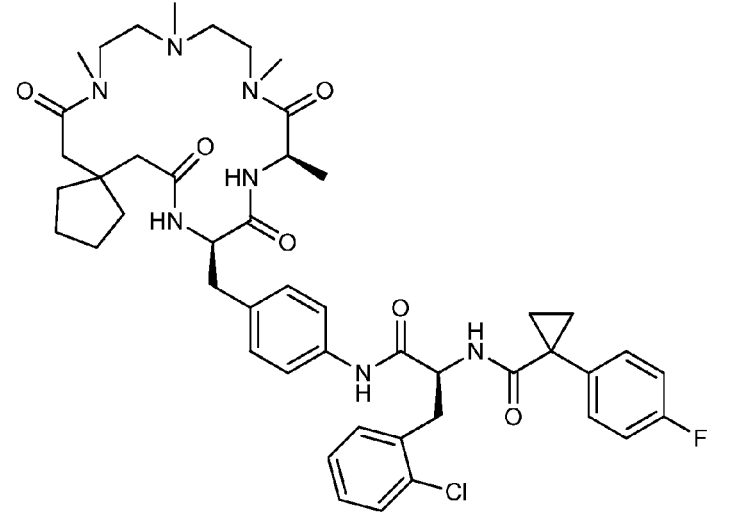
Compound No.	Structure
562	 <p>Chemical structure of Compound 562. It features a macrocyclic ring system with two tertiary amine groups (N-methyl) and two carbonyl groups. The macrocycle is linked via amide bonds to a side chain. The side chain includes a cyclopentyl group, a benzyl group, a 2-chlorophenyl group, a 4-(dimethylaminomethyl)benzyl group, and a 4-(dimethylaminomethyl)benzyl group.</p>
563	 <p>Chemical structure of Compound 563. It features a macrocyclic ring system with two tertiary amine groups (N-methyl) and two carbonyl groups. The macrocycle is linked via amide bonds to a side chain. The side chain includes a cyclopentyl group, a benzyl group, a 2-chlorophenyl group, a 4-(dimethylaminomethyl)benzyl group, and a 4-(dimethylaminomethyl)benzyl group.</p>

FIG. 12-215

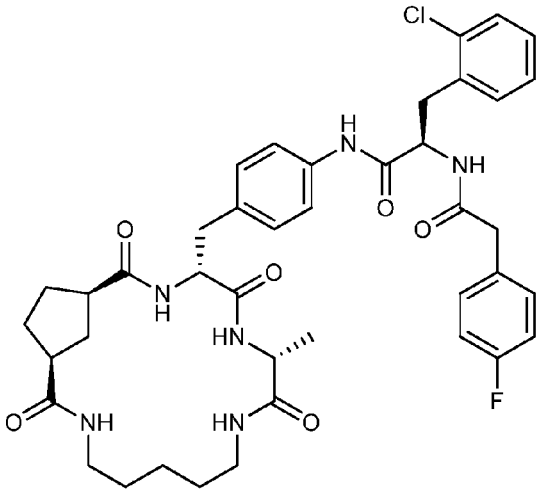
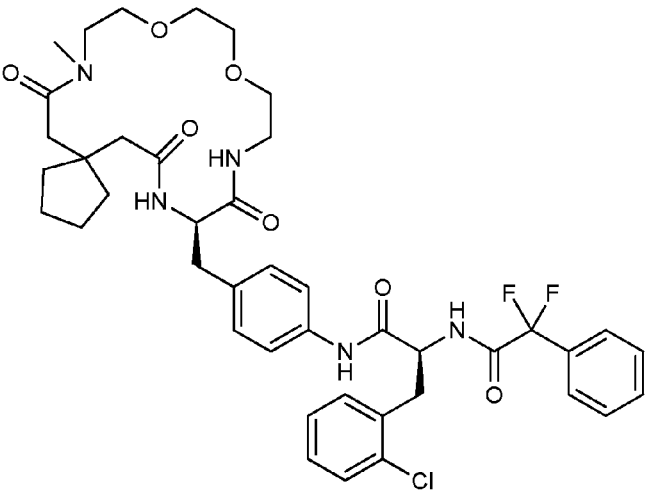
Compound No.	Structure
564	 <p>Chemical structure of Compound 564: A macrocyclic amide with a 10-membered ring containing four amide groups. The ring is substituted with a 4-(4-chlorobenzoylamino)-2-(4-(4-fluorobenzoylamino)-2-methylpropanamido)phenyl group. The structure includes a 4-chlorophenyl group, a 4-fluorophenyl group, and a 2-methylpropanamido group.</p>
565	 <p>Chemical structure of Compound 565: A complex molecule featuring a 10-membered macrocyclic amide ring. The ring is substituted with a 4-(4-chlorobenzoylamino)-2-(4-(4-fluorobenzoylamino)-2-methylpropanamido)phenyl group. The structure includes a 4-chlorophenyl group, a 4-fluorophenyl group, and a 2-methylpropanamido group.</p>

FIG. 12-216

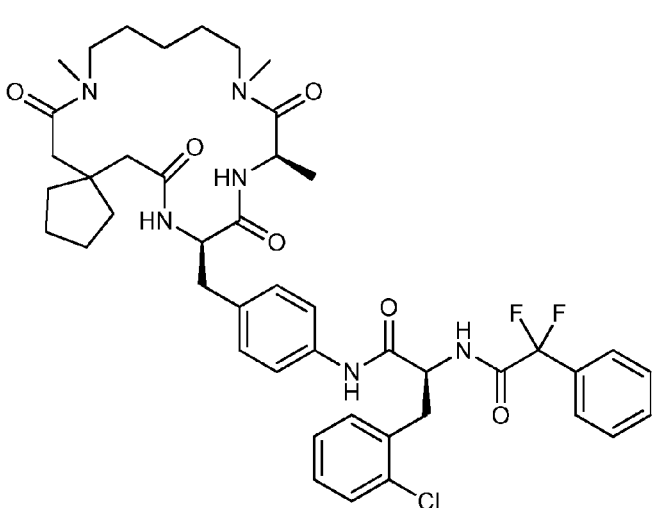
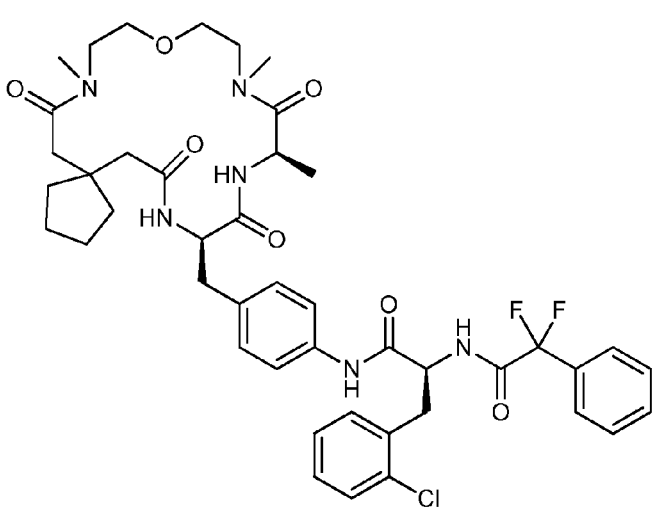
Compound No.	Structure
566	 <p>Chemical structure of Compound 566: A complex molecule featuring a macrocyclic ring system. The macrocycle contains two amide groups and a cyclopentyl ring. It is linked via a chiral center to a side chain containing a benzamide group, a 3-chlorophenyl group, and a 1,1-difluoro-2-phenylethyl group.</p>
567	 <p>Chemical structure of Compound 567: A complex molecule featuring a macrocyclic ring system. The macrocycle contains two amide groups and a cyclopentyl ring. It is linked via a chiral center to a side chain containing a benzamide group, a 3-chlorophenyl group, and a 1,1-difluoro-2-phenylethyl group. The structure is identical to Compound 566, but the macrocyclic ring system is a 1,3-dioxane derivative instead of a 1,3-dioxane derivative.</p>

FIG. 12-217

Compound No.	Structure
568	
569	

FIG. 12-218

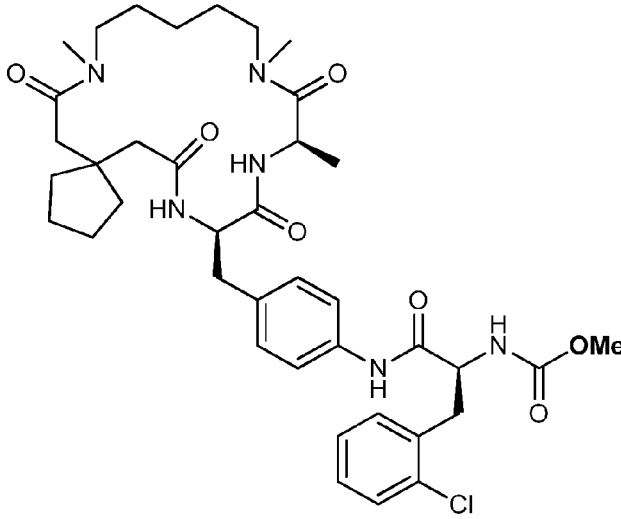
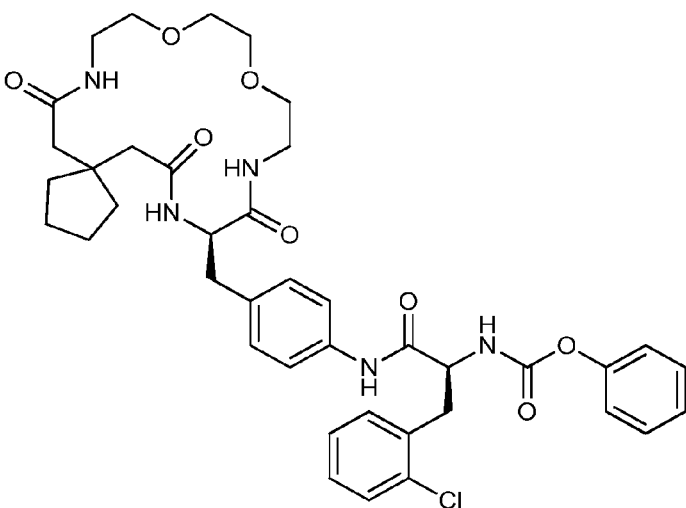
Compound No.	Structure
570	 <p>Chemical structure of Compound 570: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain includes a 4-((2-chlorophenyl)amino)phenyl group and a methyl ester group (OMe).</p>
571	 <p>Chemical structure of Compound 571: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide bonds. The chain includes a 4-((2-chlorophenyl)amino)phenyl group and a benzoyl group (C(=O)O-C6H5).</p>

FIG. 12-219

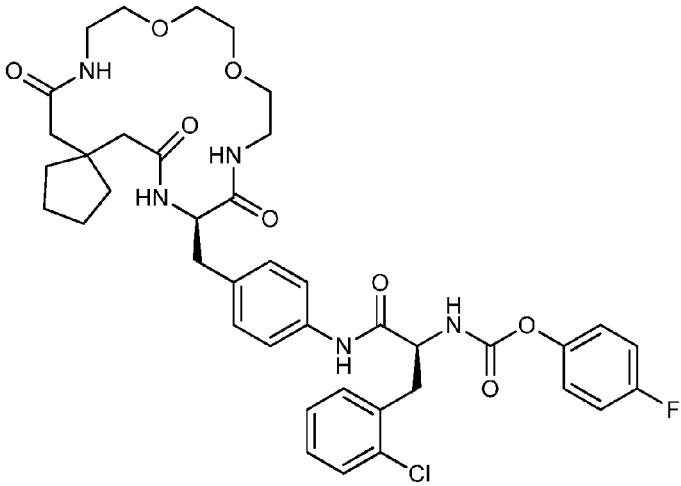
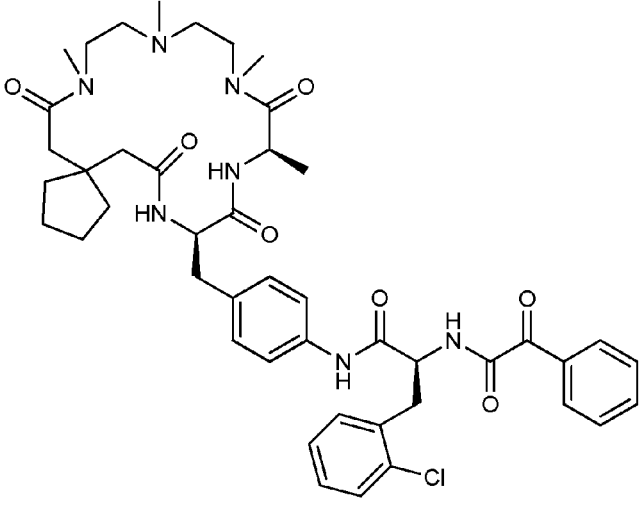
Compound No.	Structure
572	 <p>Chemical structure of Compound 572: A complex molecule featuring a cyclopentyl ring connected to a chain containing a carbamate group, a secondary amide, and a tertiary amide. The chain is further substituted with a 4-chlorophenyl group and a 4-fluorophenyl group.</p>
573	 <p>Chemical structure of Compound 573: A complex molecule featuring a cyclopentyl ring connected to a chain containing a carbamate group, a secondary amide, and a tertiary amide. The chain is further substituted with a 4-chlorophenyl group and a 4-fluorophenyl group.</p>

FIG. 12-220

[illegible]

FIG. 12-221

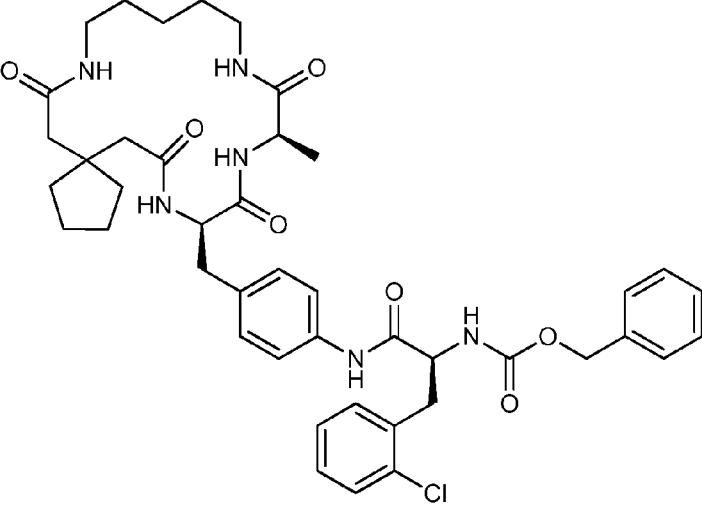
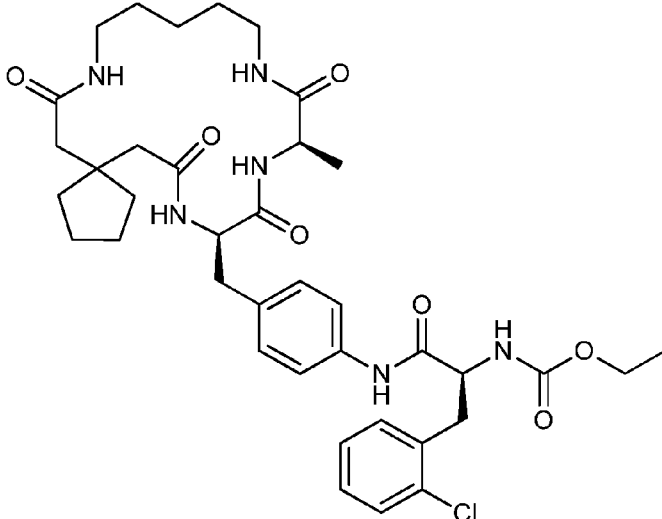
Compound No.	Structure
576	 <p>Chemical structure of Compound 576: A complex molecule featuring a 1,4-bis(amide)heptane chain. One amide is attached to a cyclopentylmethyl group, and the other is attached to a chiral center (C1) which is also bonded to a methyl group and an amide group. This amide group is further substituted with a 4-(2-chlorobenzyl)phenyl group and a benzyl group. The benzyl group is attached to a chiral center (C2) which is also bonded to a methyl group and an amide group. This amide group is further substituted with a benzyl group and a benzyl ester group.</p>
577	 <p>Chemical structure of Compound 577: A complex molecule featuring a 1,4-bis(amide)heptane chain. One amide is attached to a cyclopentylmethyl group, and the other is attached to a chiral center (C1) which is also bonded to a methyl group and an amide group. This amide group is further substituted with a 4-(2-chlorobenzyl)phenyl group and a benzyl group. The benzyl group is attached to a chiral center (C2) which is also bonded to a methyl group and an amide group. This amide group is further substituted with a benzyl group and an ethyl ester group.</p>

FIG. 12-222

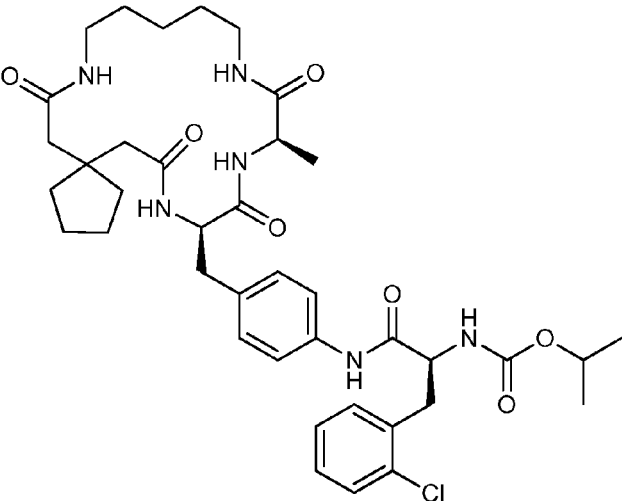
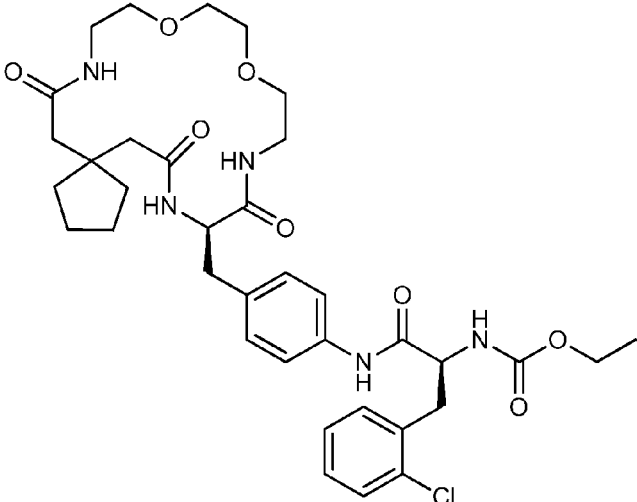
Compound No.	Structure
578	 <p>Chemical structure of Compound 578: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide groups. The chain is further substituted with a benzyl group, a 4-chlorophenyl group, and an isopropyl ester group.</p>
579	 <p>Chemical structure of Compound 579: A complex molecule featuring a cyclopentyl ring connected to a chain containing two amide groups. The chain is further substituted with a benzyl group, a 4-chlorophenyl group, and an ethyl ester group.</p>

FIG. 12-223

Compound No.	Structure
580	
581	

FIG. 12-224

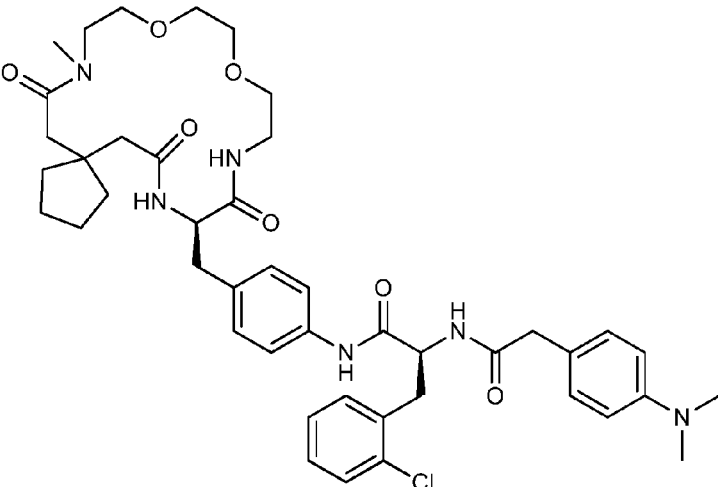
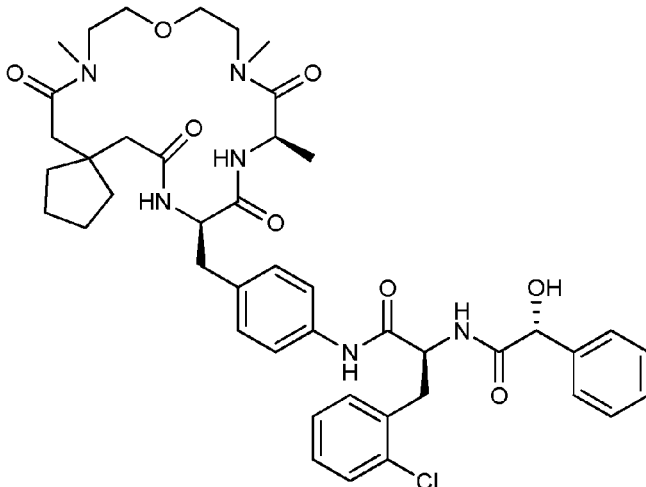
Compound No.	Structure
582	 <p>Chemical structure of Compound 582. It features a macrocyclic ring system with a cyclopentyl group and a dimethylamino group. The macrocycle is linked via amide bonds to a side chain containing a 4-chlorophenyl group, a 2-chlorophenyl group, and a dimethylaminomethyl group.</p>
583	 <p>Chemical structure of Compound 583. It features a macrocyclic ring system with a cyclopentyl group and a dimethylamino group. The macrocycle is linked via amide bonds to a side chain containing a 4-chlorophenyl group, a 2-chlorophenyl group, and a hydroxymethyl group.</p>

FIG. 12-225

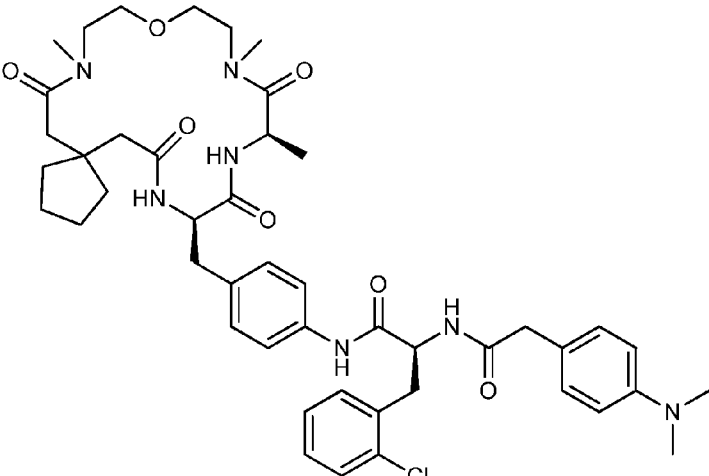
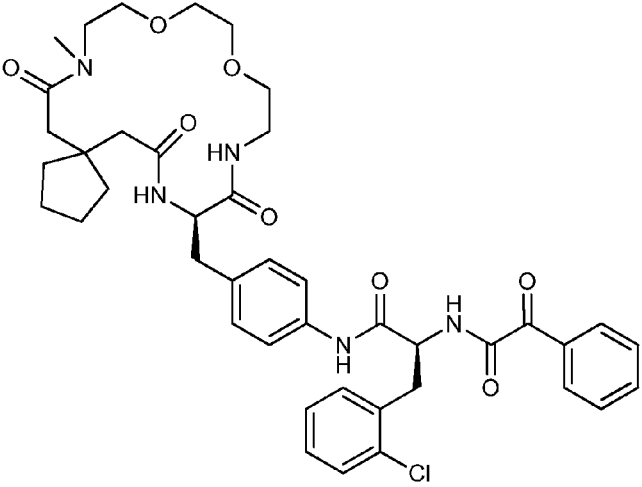
Compound No.	Structure
584	 <p>Chemical structure of Compound 584. It features a 1,3-bis(methylamino)propan-2-yl group connected via an amide bond to a cyclopentylmethyl group. This cyclopentylmethyl group is further connected via an amide bond to a 1-(2-chlorophenyl)-2-((4-(dimethylaminomethyl)benzoyl)amino)ethyl group. The 2-chlorophenyl ring is substituted with a 2-chlorophenyl group at the 1-position and a 4-(dimethylaminomethyl)benzoyl group at the 2-position.</p>
585	 <p>Chemical structure of Compound 585. It features a 1,3-bis(methylamino)propan-2-yl group connected via an amide bond to a cyclopentylmethyl group. This cyclopentylmethyl group is further connected via an amide bond to a 1-(2-chlorophenyl)-2-((4-benzoylamino)benzoyl)amino)ethyl group. The 2-chlorophenyl ring is substituted with a 2-chlorophenyl group at the 1-position and a 4-benzoylamino group at the 2-position.</p>

FIG. 12-226

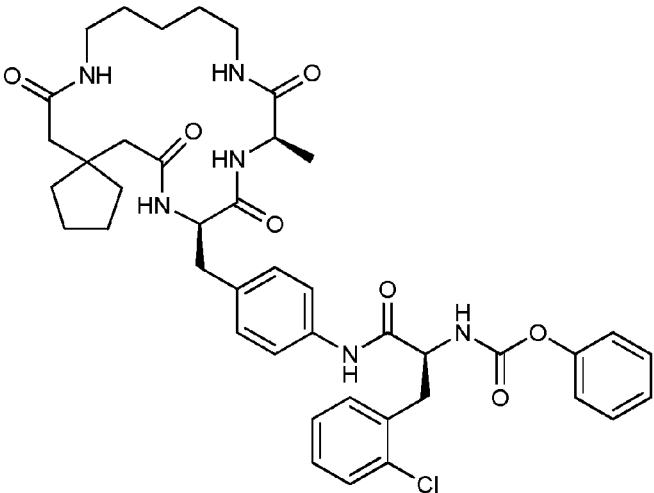
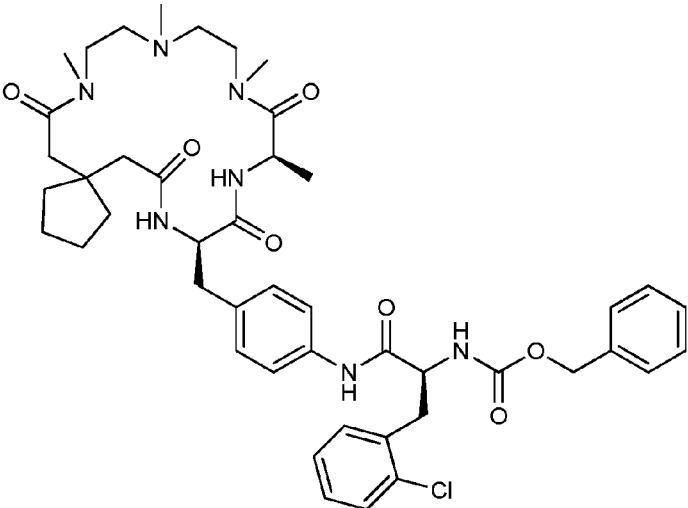
Compound No.	Structure
586	 <p>Chemical structure of Compound 586: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide. This amide chain includes a benzyl group, a 2-chlorophenyl group, and a benzyloxycarbonyl (Boc) protecting group. The structure is drawn with stereochemical wedges and dashes to indicate the 3D arrangement of the substituents.</p>
587	 <p>Chemical structure of Compound 587: Similar to Compound 586, but the long-chain amide is substituted with a dimethylamino group instead of a long-chain amide. The structure is drawn with stereochemical wedges and dashes to indicate the 3D arrangement of the substituents.</p>

FIG. 12-227

Compound No.	Structure
588	
589	

FIG. 12-228

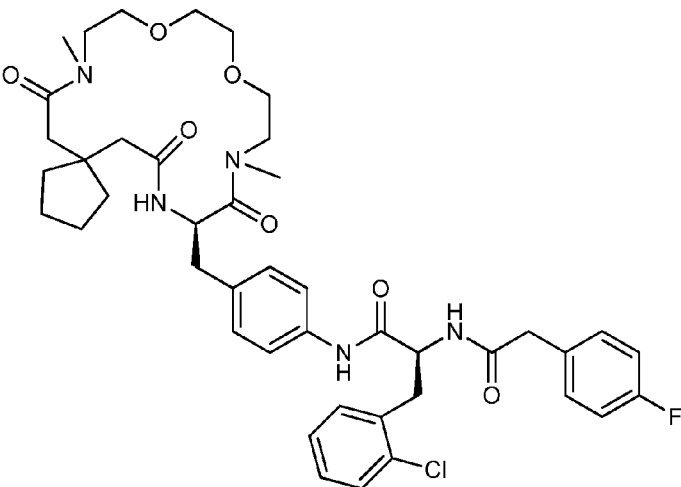
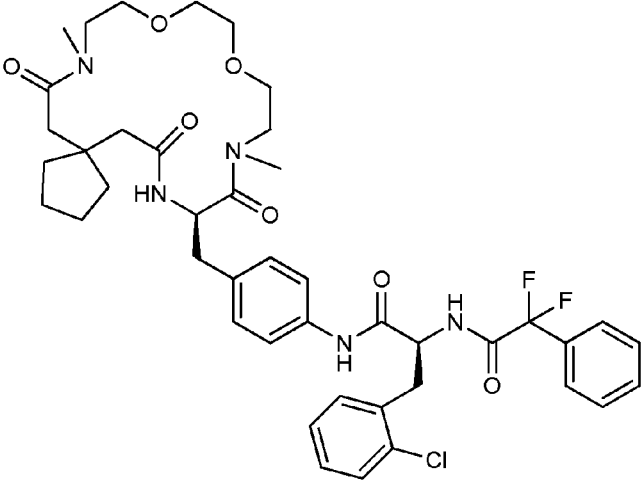
Compound No.	Structure
590	 <p>Chemical structure of Compound 590. The molecule features a complex polycyclic system. It includes a cyclopentane ring fused to a piperidine ring, which is further substituted with a long chain containing multiple amide and ether linkages. A 4-fluorophenyl group is attached to the chain, and a 2-chlorophenyl group is attached to the piperidine ring.</p>
591	 <p>Chemical structure of Compound 591. The molecule features a complex polycyclic system. It includes a cyclopentane ring fused to a piperidine ring, which is further substituted with a long chain containing multiple amide and ether linkages. A 2-chlorophenyl group is attached to the piperidine ring, and a 4-fluorophenyl group is attached to the chain.</p>

FIG. 12-229

Compound No.	Structure
592	
593	

FIG. 12-230

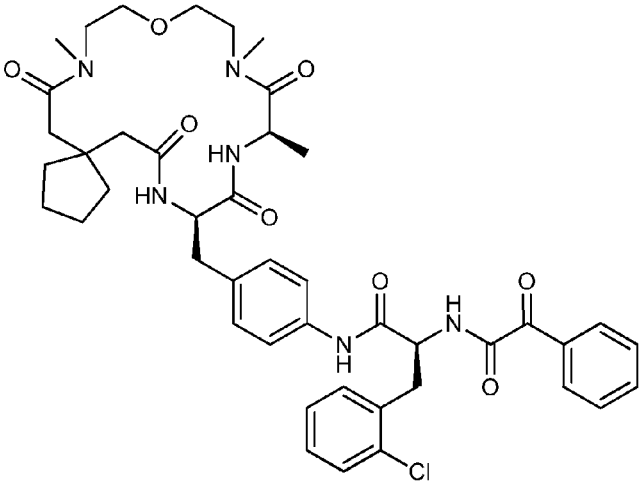
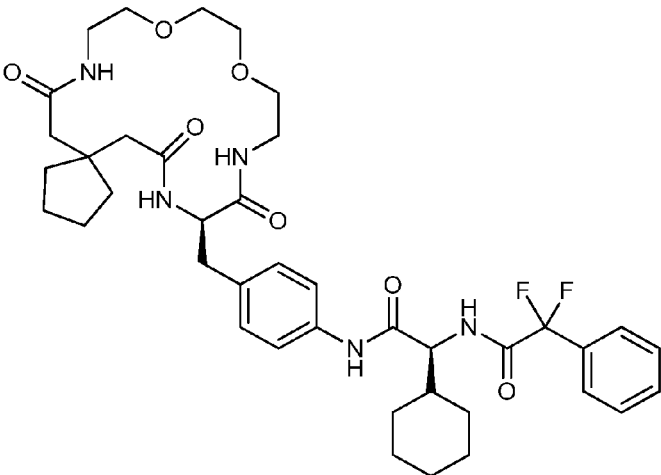
Compound No.	Structure
594	 <p>Chemical structure of Compound 594. It features a macrocyclic ring system with two nitrogen atoms and an oxygen atom. The macrocycle is substituted with a cyclopentyl group and a chiral center. A side chain extends from the macrocycle, containing a benzamide group, a chiral center, and a benzoyl group.</p>
595	 <p>Chemical structure of Compound 595. It features a macrocyclic ring system with two nitrogen atoms and an oxygen atom. The macrocycle is substituted with a cyclopentyl group and a chiral center. A side chain extends from the macrocycle, containing a benzamide group, a chiral center, and a benzoyl group with a fluorine substituent.</p>

FIG. 12-231

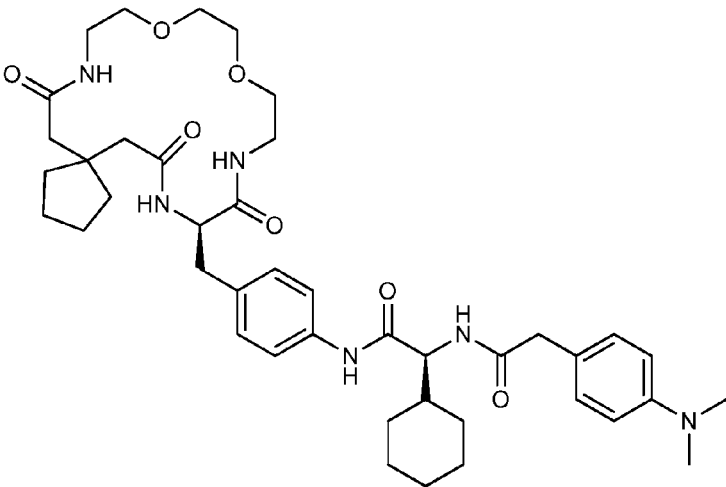
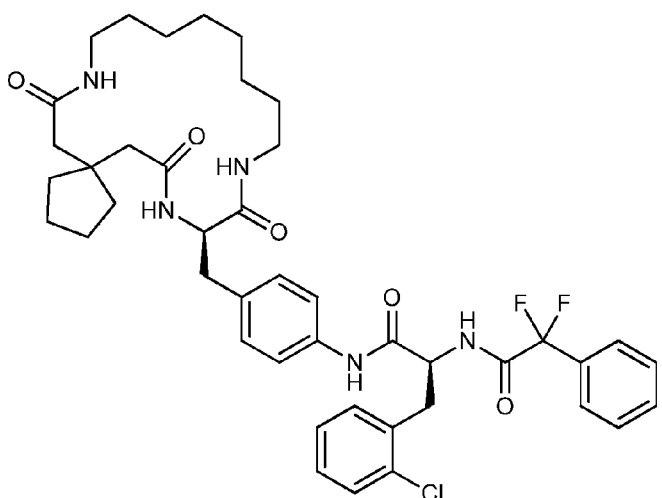
Compound No.	Structure
596	 <p>Chemical structure of Compound 596: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group) linked via a chiral center to a benzamide moiety. This benzamide is further linked to a cyclohexyl group, which is connected to a dimethylaminophenyl group through a series of amide and ester linkages.</p>
597	 <p>Chemical structure of Compound 597: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a six-membered ring with an amide group) linked via a chiral center to a benzamide moiety. This benzamide is further linked to a 3-chlorophenyl group, which is connected to a 2,2-difluorophenyl group through a series of amide and ester linkages.</p>

FIG. 12-232

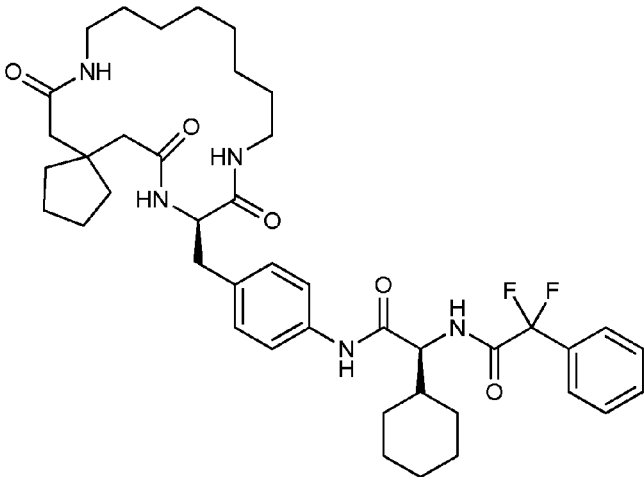
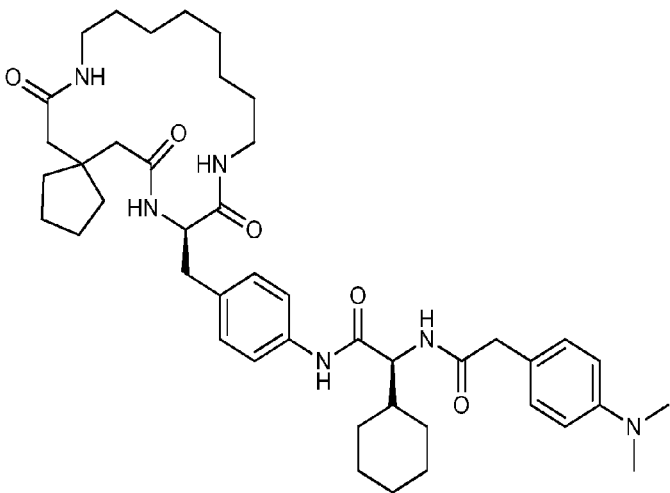
Compound No.	Structure
598	 <p>Chemical structure of Compound 598: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide group). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a cyclohexyl group and a difluoromethyl group, which is in turn linked to a phenyl ring.</p>
599	 <p>Chemical structure of Compound 599: A complex molecule featuring a bicyclic amide system (a cyclopentane ring fused to a six-membered ring containing an amide group). This system is linked via a chiral center to a benzamide moiety. The benzamide is further connected to a cyclohexyl group and a dimethylaminomethyl group, which is in turn linked to a phenyl ring.</p>

FIG. 12-233

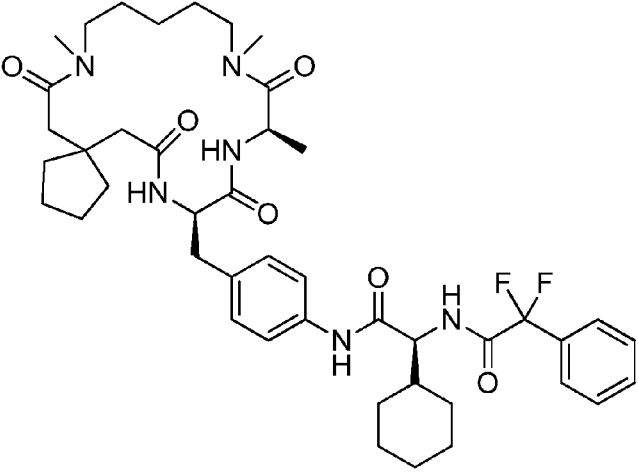
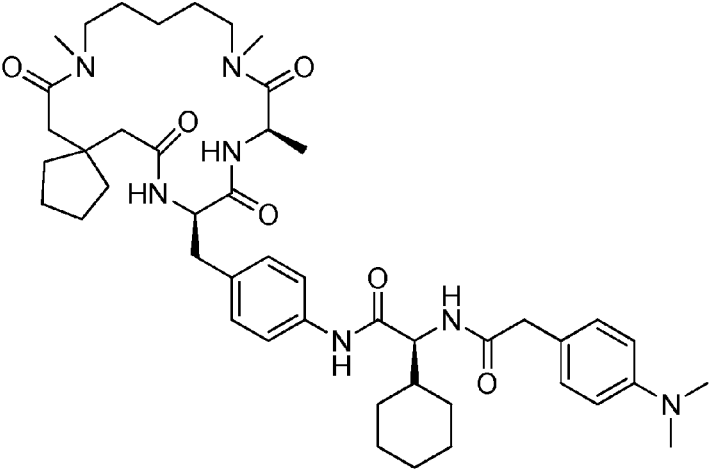
Compound No.	Structure
600	 <p>Chemical structure of Compound 600. It features a macrocyclic core with two N-methyl-N-(cyclopentylmethyl)acetamido groups. The macrocycle is substituted with a (S)-1-((4-((S)-1-((S)-1-(2-fluorophenyl)-2-fluoroethyl)amino)-1-cyclohexyl)ethanone)benzyl)pyrrolidine-2-carboxamide group.</p>
601	 <p>Chemical structure of Compound 601. It features a macrocyclic core with two N-methyl-N-(cyclopentylmethyl)acetamido groups. The macrocycle is substituted with a (S)-1-((4-((S)-1-((S)-1-(4-(dimethylaminophenyl)ethyl)amino)-1-cyclohexyl)ethanone)benzyl)pyrrolidine-2-carboxamide group.</p>

FIG. 12-234

Compound No.	Structure
602	
603	

FIG. 12-235

Compound No.	Structure
604	
605	

FIG. 12-236

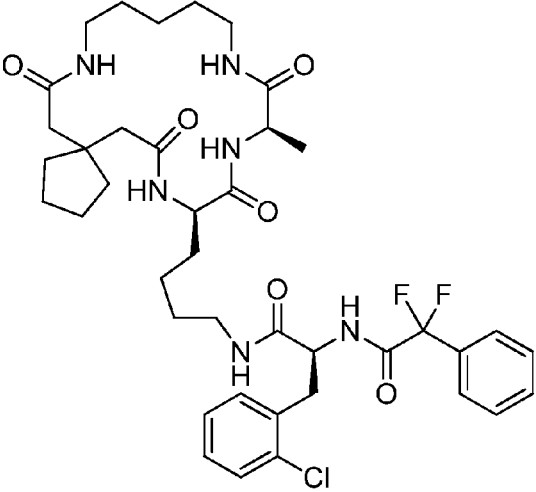
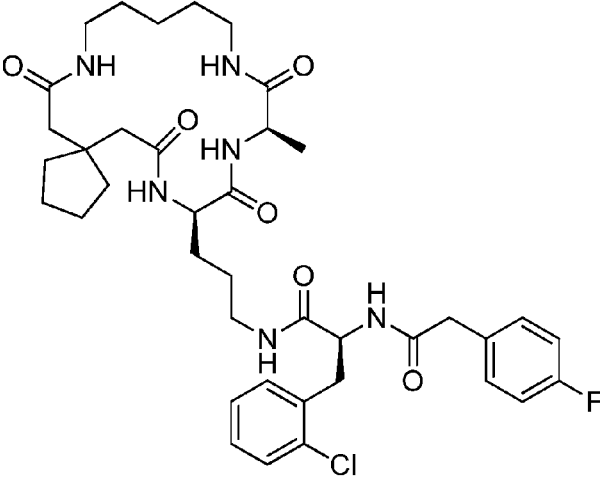
Compound No.	Structure
606	 <p>Chemical structure of compound 606. It features a complex polycyclic amide system. A cyclopentane ring is fused to a six-membered ring containing two amide groups. This system is connected via a chain to another six-membered ring with an amide group and a chlorine substituent. A side chain with a trifluoromethyl group is also present.</p>
607	 <p>Chemical structure of compound 607. It features a complex polycyclic amide system, similar to compound 606, but with a different side chain. The side chain includes a benzamide moiety with a fluorine substituent on the benzene ring.</p>

FIG. 12-237

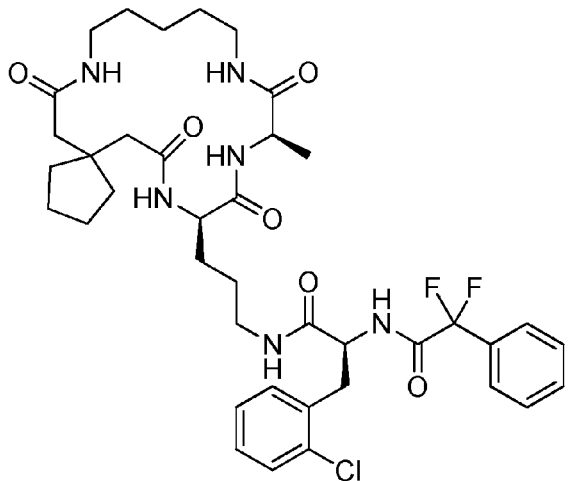
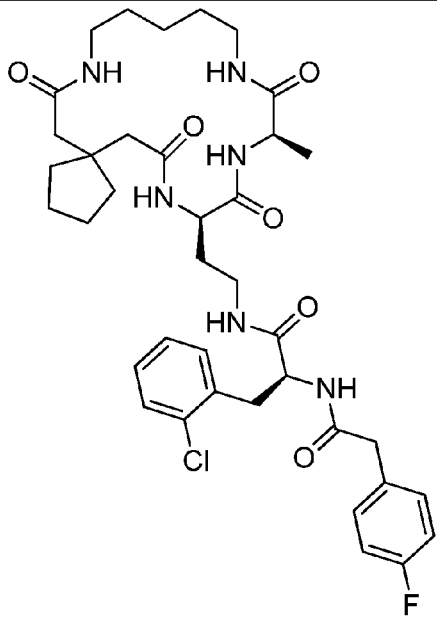
Compound No.	Structure
608	 <p>Chemical structure of Compound 608. It features a complex polycyclic amide system. A cyclopentane ring is fused to a six-membered ring containing two amide groups. This system is connected via a chiral center to a side chain that includes a benzamide moiety with a 3-chlorophenyl group and a 2,2-difluoro-1-phenylethan-1-yl group.</p>
609	 <p>Chemical structure of Compound 609. It features a complex polycyclic amide system similar to Compound 608. A cyclopentane ring is fused to a six-membered ring containing two amide groups. This system is connected via a chiral center to a side chain that includes a benzamide moiety with a 3-chlorophenyl group and a 4-fluorophenyl group.</p>

FIG. 12-238

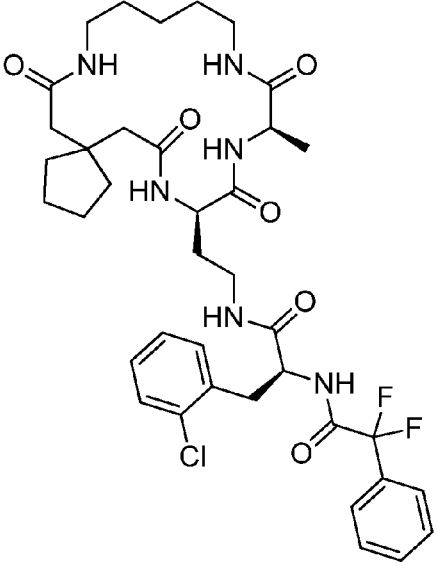
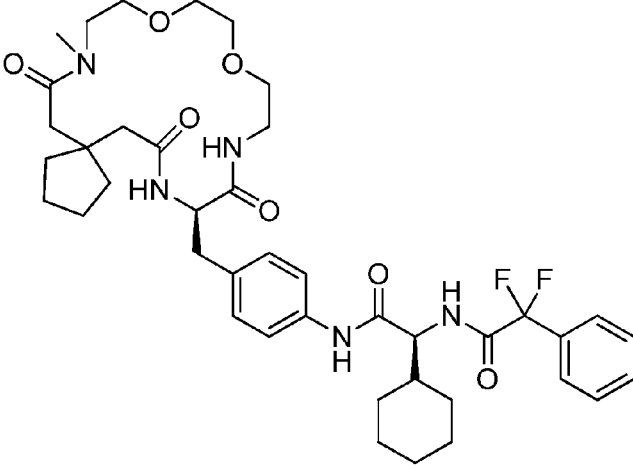
Compound No.	Structure
610	 <p>Chemical structure of Compound 610: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide. This amide chain includes a chiral center with a methyl group and a side chain containing a 3-chlorophenyl group and a 1,1-difluoro-2-phenylethyl group.</p>
611	 <p>Chemical structure of Compound 611: A complex molecule featuring a cyclopentane ring substituted with a long-chain amide. This amide chain includes a chiral center with a cyclohexyl group and a side chain containing a 4-((1,1-difluoro-2-phenylethyl)amino)phenyl group.</p>

FIG. 12-239

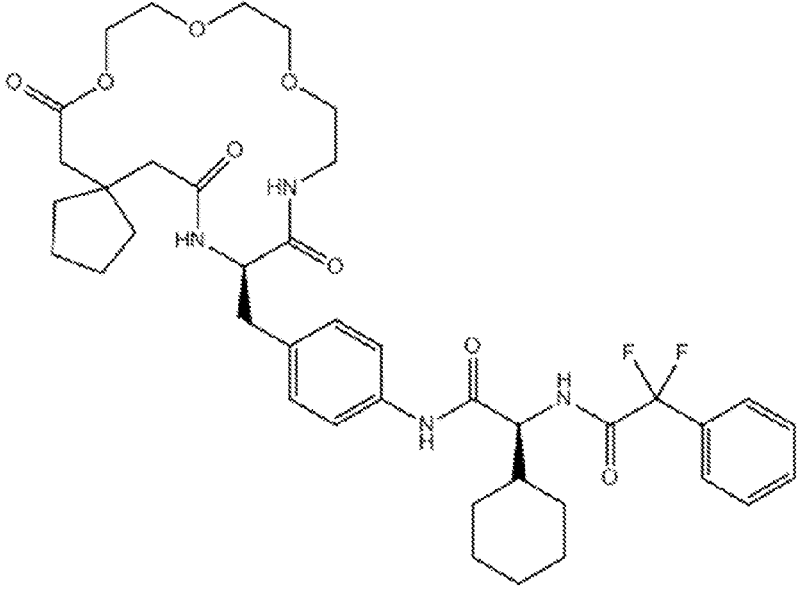
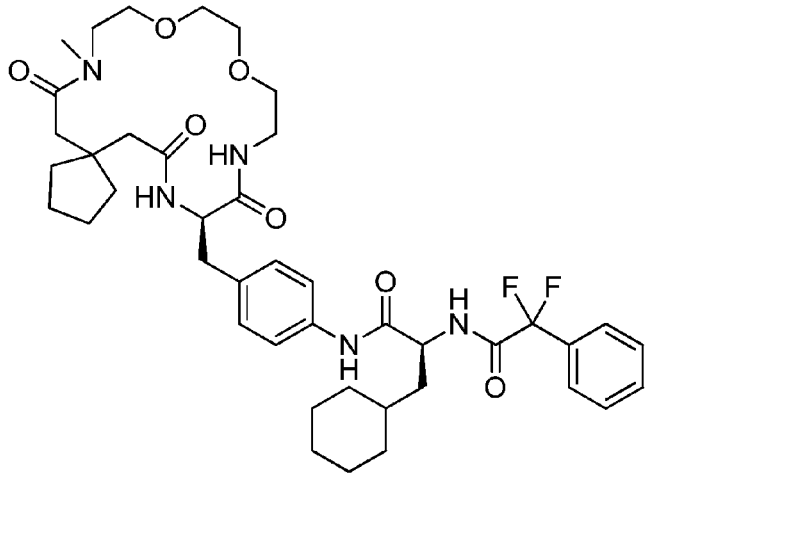
Compound No.	Structure
612	 <p>Chemical structure of Compound 612. It features a 10-membered cyclic urea with a cyclopentyl group and a carbonyl group. This is linked via a chiral center to a benzyl group, which is further linked to a cyclohexyl group. The structure also includes a trifluoromethyl group and a benzyl group.</p>
613	 <p>Chemical structure of Compound 613. It features a 10-membered cyclic urea with a cyclopentyl group and a carbonyl group. This is linked via a chiral center to a benzyl group, which is further linked to a cyclohexyl group. The structure also includes a trifluoromethyl group and a benzyl group.</p>

FIG. 12-240

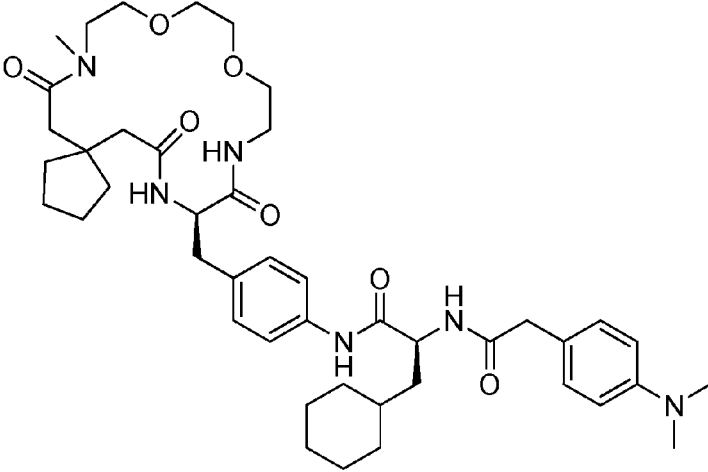
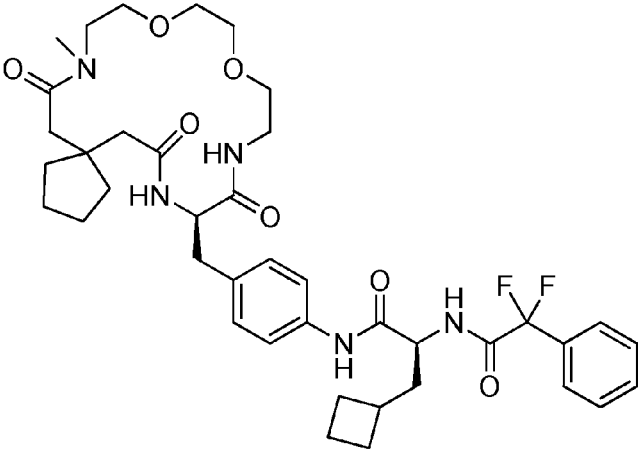
Compound No.	Structure
614	 <p>Chemical structure of Compound 614. It features a complex molecule with a central cyclohexane ring. Attached to this ring is a side chain containing a benzamide group, which is further substituted with a dimethylaminomethyl group. The molecule also includes a large, complex ring system on the left side, featuring a nitrogen atom and several oxygen atoms, suggesting a macrocyclic or cyclic ether structure. The overall structure is highly branched and contains multiple amide and ether linkages.</p>
615	 <p>Chemical structure of Compound 615. It features a complex molecule with a central cyclohexane ring. Attached to this ring is a side chain containing a benzamide group, which is further substituted with a dimethylaminomethyl group. The molecule also includes a large, complex ring system on the left side, featuring a nitrogen atom and several oxygen atoms, suggesting a macrocyclic or cyclic ether structure. The overall structure is highly branched and contains multiple amide and ether linkages.</p>

FIG. 12-241

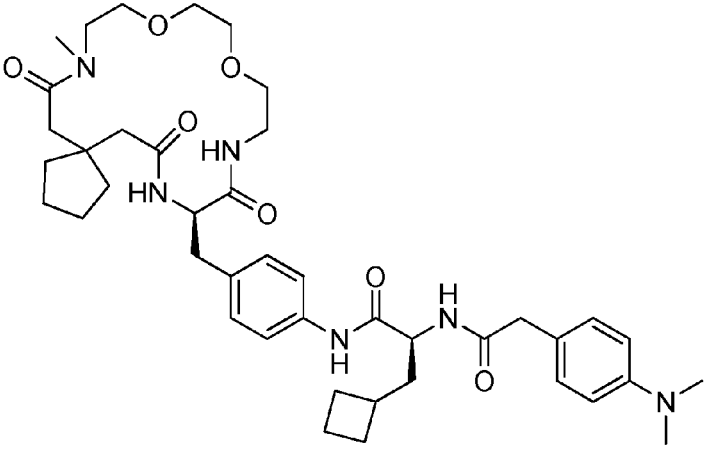
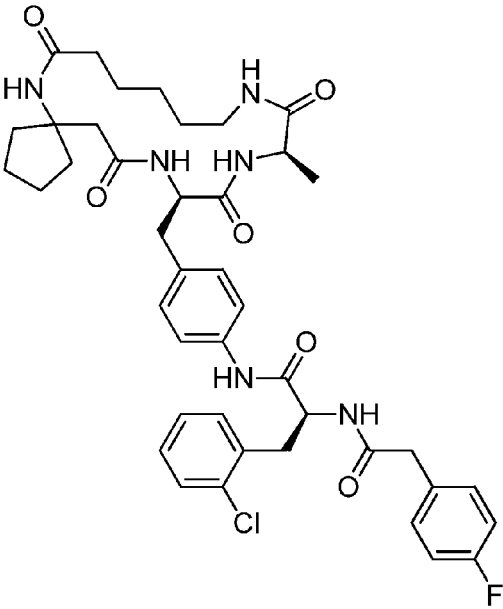
Compound No.	Structure
616	 <p>Chemical structure of Compound 616: A complex molecule featuring a cyclopentyl ring connected to a chain containing a morpholine ring, a benzamide group, a cyclobutyl ring, and a dimethylaminophenyl group.</p>
617	 <p>Chemical structure of Compound 617: A complex molecule featuring a cyclopentyl ring connected to a chain containing a benzamide group, a chlorophenyl group, and a 4-fluorophenyl group.</p>

FIG. 12-242

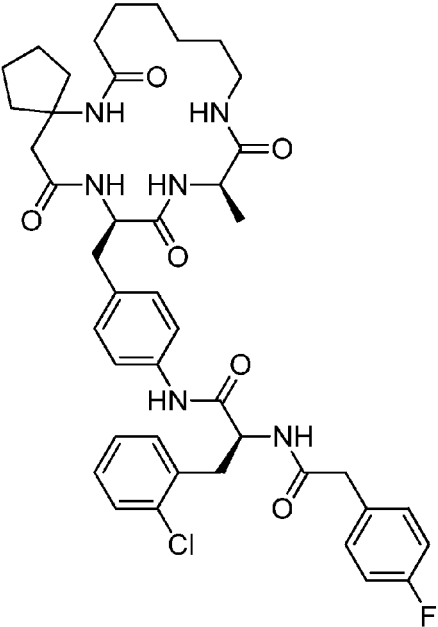
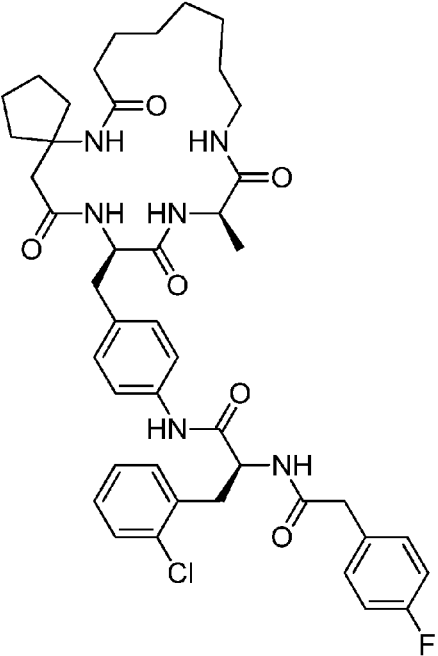
Compound No.	Structure
618	 <p>Chemical structure of Compound 618. It features a bicyclic amide system (a cyclohexane ring fused to a cyclopentane ring) connected via an amide bond to a side chain. The side chain includes a benzamide moiety, a 3-chlorophenyl group, and a 4-fluorophenyl group.</p>
619	 <p>Chemical structure of Compound 619. It is identical to Compound 618, featuring a bicyclic amide system connected via an amide bond to a side chain. The side chain includes a benzamide moiety, a 3-chlorophenyl group, and a 4-fluorophenyl group.</p>

FIG. 12-243

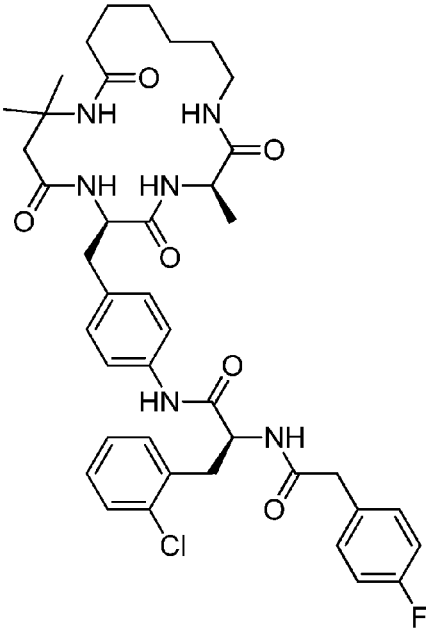
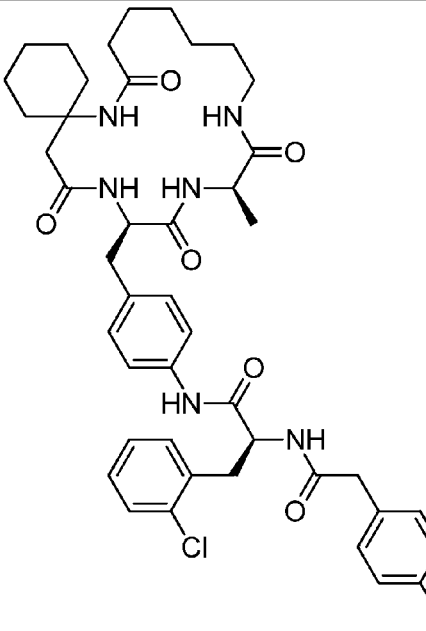
Compound No.	Structure
620	 <p>Chemical structure of Compound 620: A complex molecule featuring a bicyclic amide system (a cyclohexane ring fused to a seven-membered ring containing two amide groups). This system is linked via a carbonyl group to a chain containing a benzamide moiety, a 3-chlorophenyl group, and a 4-fluorophenyl group.</p>
621	 <p>Chemical structure of Compound 621: A complex molecule featuring a bicyclic amide system (a cyclohexane ring fused to a seven-membered ring containing two amide groups). This system is linked via a carbonyl group to a chain containing a benzamide moiety, a 3-chlorophenyl group, and a 4-fluorophenyl group. The structure is identical to Compound 620.</p>

FIG. 12-244

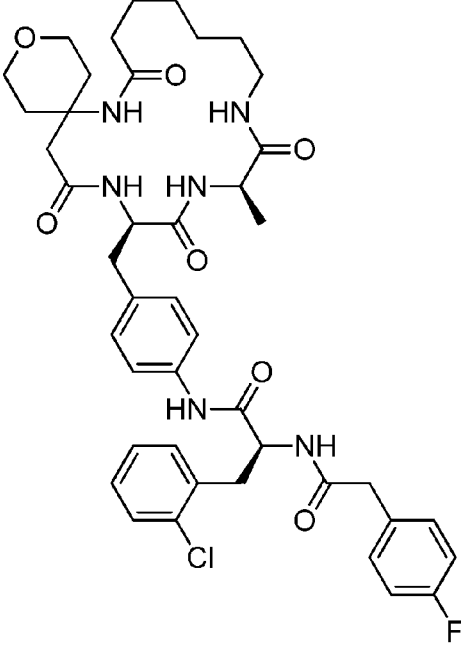
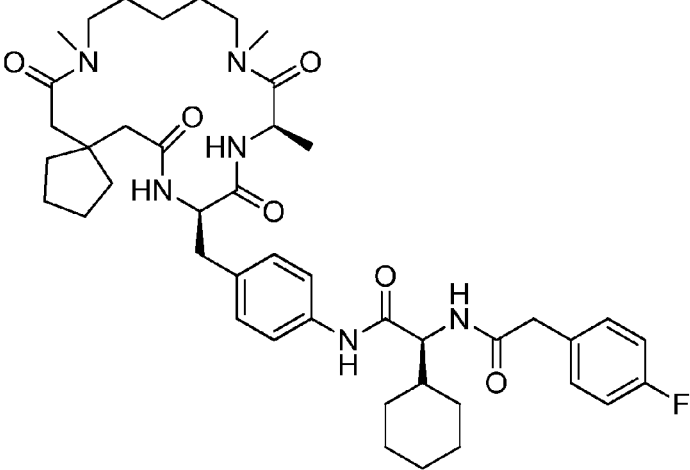
Compound No.	Structure
622	 <p>Chemical structure of compound 622. It features a morpholine ring connected to a complex amide system. The structure includes a benzamide moiety, a 3-chlorobenzamide moiety, and a 4-fluorobenzamide moiety, all linked together via amide bonds. Stereochemistry is indicated with wedges and dashes.</p>
623	 <p>Chemical structure of compound 623. It features a morpholine ring connected to a complex amide system. The structure includes a benzamide moiety, a cyclohexylamide moiety, and a 4-fluorobenzamide moiety, all linked together via amide bonds. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-245

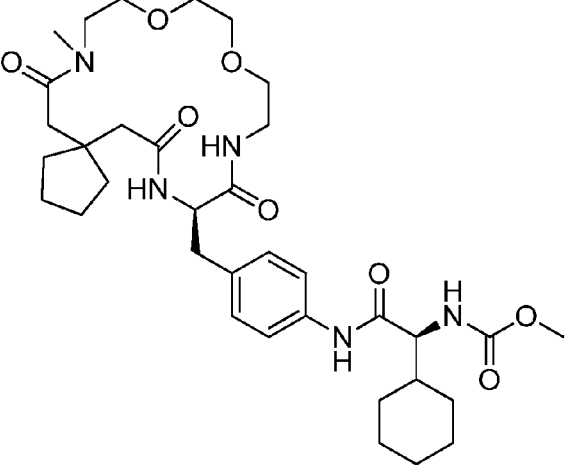
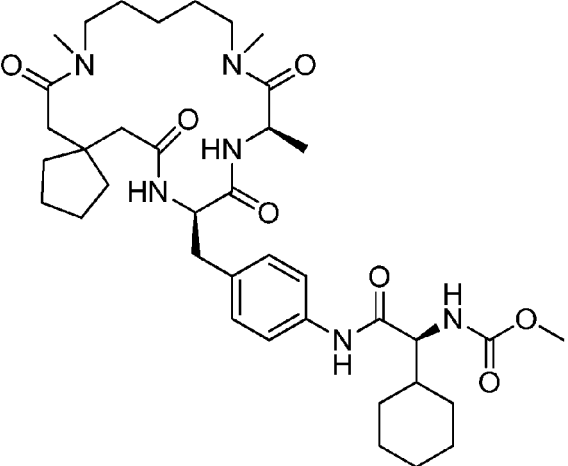
Compound No.	Structure
624	 <p>Chemical structure of Compound 624. It features a 1,3-dioxane ring system (a six-membered ring with two oxygen atoms at positions 1 and 3) substituted with a cyclopentyl group at position 4 and a carbonyl group at position 2. The carbonyl group is part of an amide linkage to a chiral center (C1) which is also bonded to a hydrogen atom and a benzyl group. The benzyl group is further substituted with a para-phenylene ring, which is linked via an amide bond to another chiral center (C2). This second chiral center is bonded to a hydrogen atom and a methoxycarbonyl group. The entire molecule is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>
625	 <p>Chemical structure of Compound 625. It features a 1,3-dioxane ring system (a six-membered ring with two oxygen atoms at positions 1 and 3) substituted with a cyclopentyl group at position 4 and a carbonyl group at position 2. The carbonyl group is part of an amide linkage to a chiral center (C1) which is also bonded to a hydrogen atom and a benzyl group. The benzyl group is further substituted with a para-phenylene ring, which is linked via an amide bond to another chiral center (C2). This second chiral center is bonded to a hydrogen atom and a methoxycarbonyl group. The entire molecule is shown in a perspective view with stereochemistry indicated by wedges and dashes.</p>

FIG. 12-246

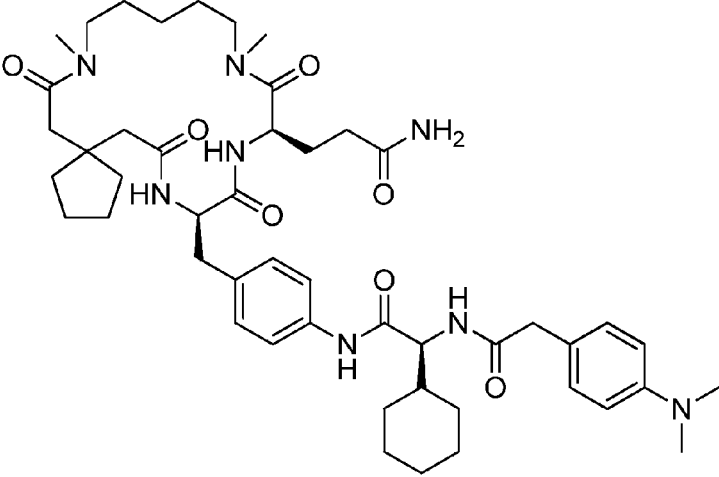
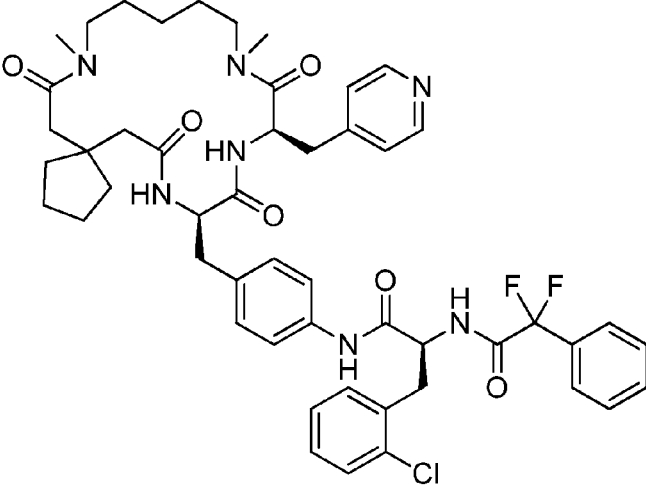
Compound No.	Structure
626	 <p>Chemical structure of Compound 626: A complex molecule featuring a macrocyclic amide ring (12-membered) with two methyl groups on the nitrogen atoms. The macrocycle is linked via amide bonds to a cyclopentyl group and a side chain containing a benzamide moiety. The benzamide is further linked to a cyclohexyl group and a dimethylaminophenyl group.</p>
627	 <p>Chemical structure of Compound 627: A complex molecule featuring a macrocyclic amide ring (12-membered) with two methyl groups on the nitrogen atoms. The macrocycle is linked via amide bonds to a cyclopentyl group and a side chain containing a pyridine moiety. The pyridine is further linked to a benzamide moiety, which is linked to a 2-chlorophenyl group and a difluoromethyl group.</p>

FIG. 12-247

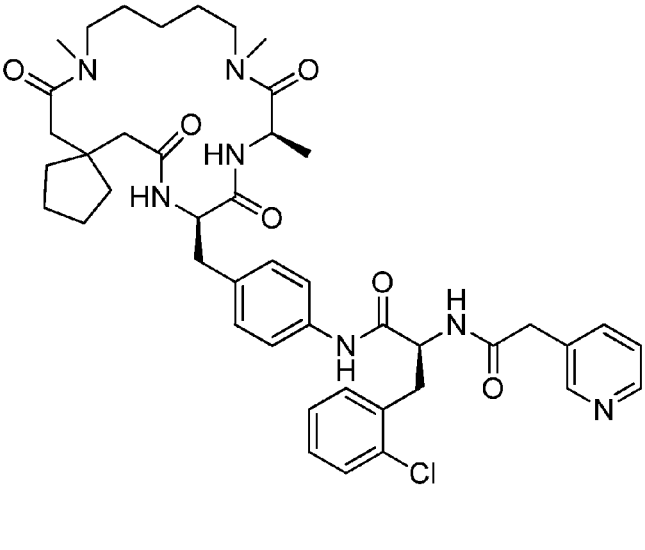
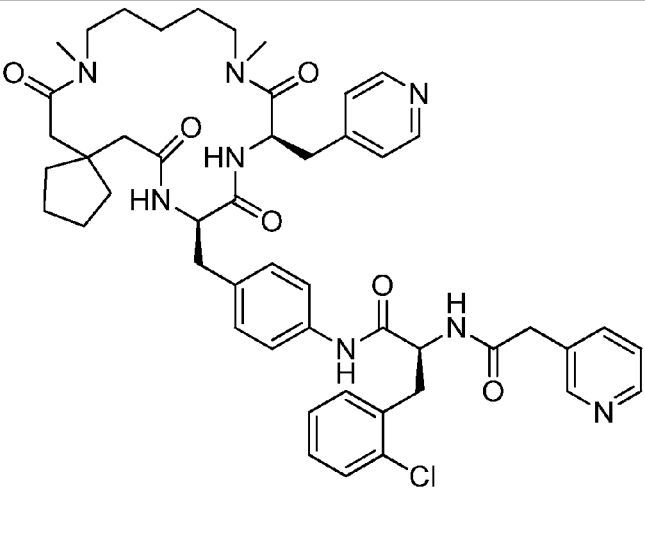
Compound No.	Structure
628	 <p>Chemical structure of Compound 628. It features a macrocyclic ring system with two N-methyl groups and two carbonyl groups. The macrocycle is linked to a cyclopentyl ring, which is further connected to a chiral center. This chiral center is part of a chain that includes a benzamide moiety, a 3-chlorophenyl group, and a pyridine ring.</p>
629	 <p>Chemical structure of Compound 629. It is similar to Compound 628, but the macrocyclic ring system is linked to a pyridine ring instead of a cyclopentyl ring.</p>

FIG. 12-248

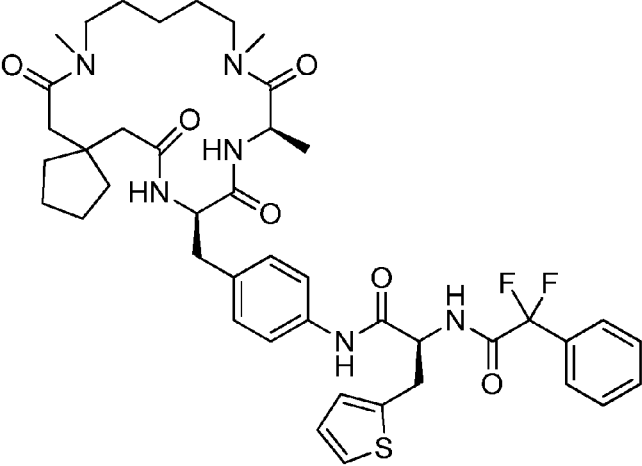
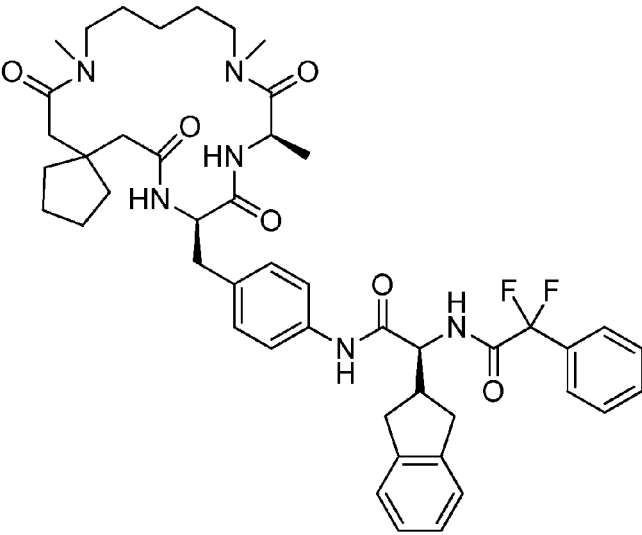
Compound No.	Structure
630	 <p>Chemical structure of Compound 630. It features a macrocyclic ring system with two tertiary amide groups (N-methyl) and two secondary amide groups. The macrocycle is substituted with a cyclopentyl group and a side chain containing a thiazole ring, a benzamide group, and a 1,1-difluoro-2-phenylethan-1-yl group.</p>
631	 <p>Chemical structure of Compound 631. It features a macrocyclic ring system with two tertiary amide groups (N-methyl) and two secondary amide groups. The macrocycle is substituted with a cyclopentyl group and a side chain containing a benzamide group and a 1,1-difluoro-2-phenylethan-1-yl group.</p>

FIG. 12-249

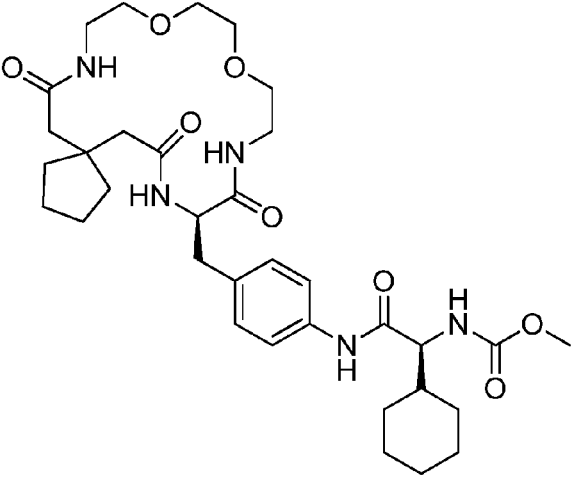
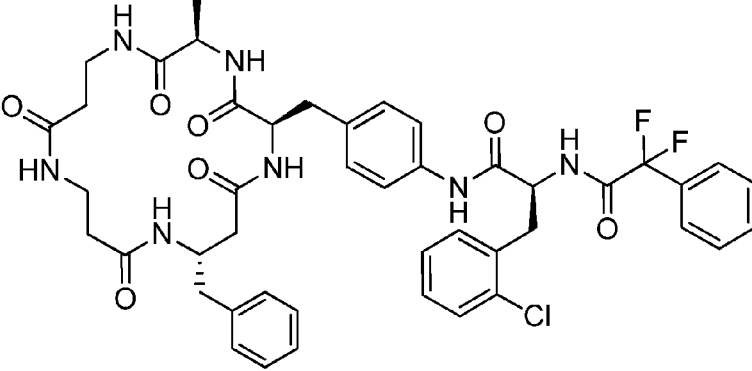
Compound No.	Structure
632	 <p>Chemical structure of Compound 632: A complex molecule featuring a 1,3-dioxane ring system fused to a cyclopentane ring. The dioxane ring is substituted with a carbonyl group and an amide linkage. The amide chain extends to a benzene ring, which is further substituted with a carbonyl group and a methoxy group. The structure is highly branched and includes multiple amide and ester functional groups.</p>
633	 <p>Chemical structure of Compound 633: A complex molecule featuring a 1,3-dioxane ring system fused to a cyclopentane ring. The dioxane ring is substituted with a carbonyl group and an amide linkage. The amide chain extends to a benzene ring, which is further substituted with a carbonyl group and a methoxy group. The structure is highly branched and includes multiple amide and ester functional groups.</p>

FIG. 12-250

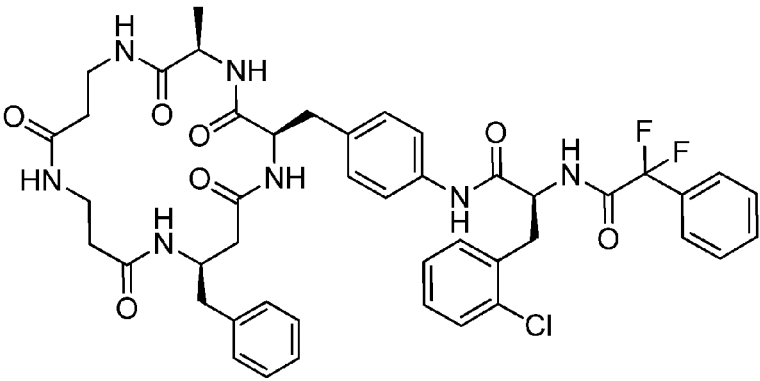
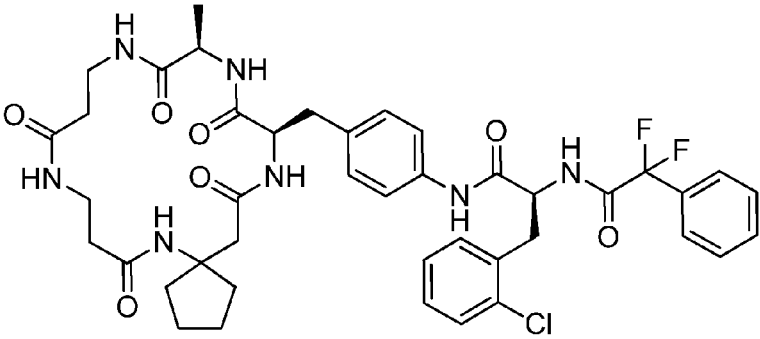
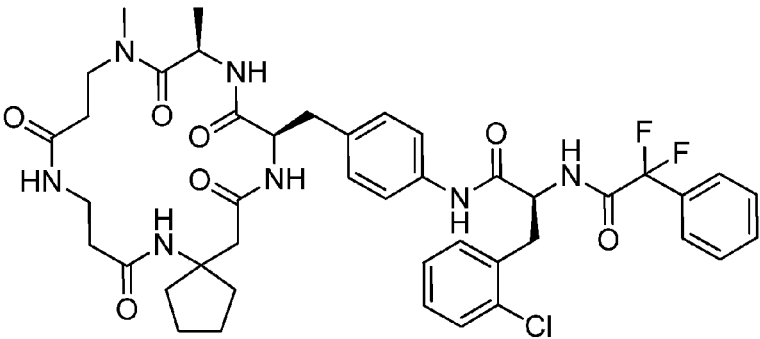
Compound No.	Structure
634	 <p>Chemical structure of compound 634. It features a central 1,4-bis(phenylmethyl)pyrrolidine-2,5-dione core. The left phenyl ring is substituted with a 2-((2S,3S)-3-((2S,3S)-3-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido)propanamido)propanamido group. The right phenyl ring is substituted with a 2-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido group. The structure includes a 2-chlorophenyl group and a 2,2-difluorophenyl group.</p>
635	 <p>Chemical structure of compound 635. It features a central 1,4-bis(phenylmethyl)pyrrolidine-2,5-dione core. The left phenyl ring is substituted with a 2-((2S,3S)-3-((2S,3S)-3-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido)propanamido)propanamido group. The right phenyl ring is substituted with a 2-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido group. The structure includes a 2-chlorophenyl group and a 2,2-difluorophenyl group.</p>
636	 <p>Chemical structure of compound 636. It features a central 1,4-bis(phenylmethyl)pyrrolidine-2,5-dione core. The left phenyl ring is substituted with a 2-((2S,3S)-3-((2S,3S)-3-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido)propanamido)propanamido group. The right phenyl ring is substituted with a 2-((2S)-2-((2S)-2-oxo-3-phenylpropanamido)propanamido)propanamido group. The structure includes a 2-chlorophenyl group and a 2,2-difluorophenyl group.</p>

FIG. 12-251

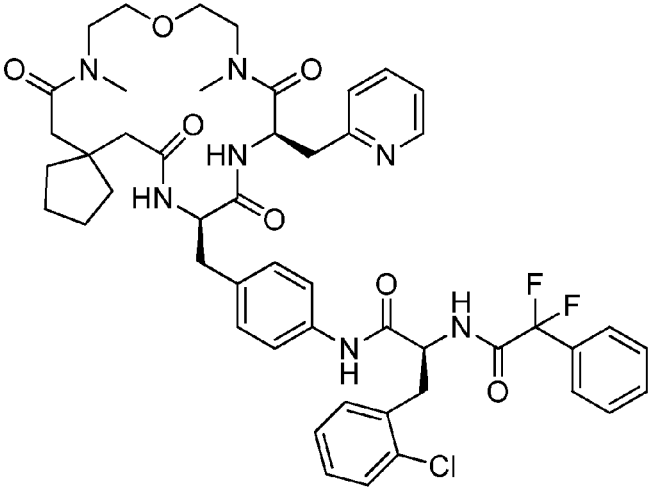
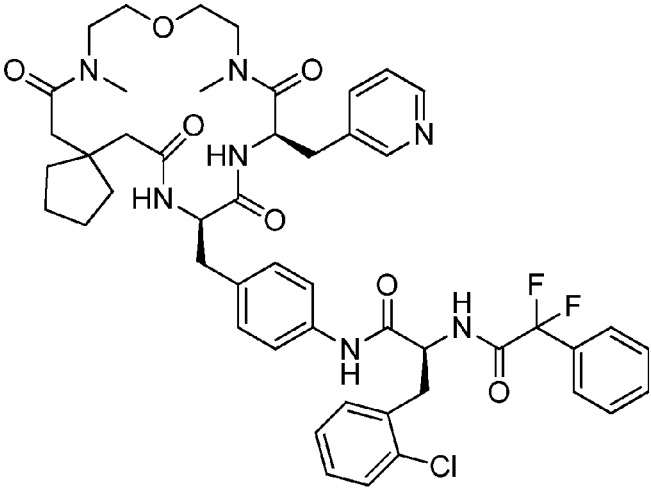
Compound No.	Structure
637	 <p>Chemical structure of compound 637. It features a 1,3-dioxane ring system. One nitrogen of the dioxane is substituted with a 2-pyridylmethyl group. The other nitrogen is part of a cyclic amide fused to a cyclopentane ring. A side chain is attached to the cyclopentane ring, consisting of a methylene group, a carbonyl group, and an amide linkage to a 4-phenyl group. This phenyl group is further substituted with a 2-chlorophenyl group and a 2,2-difluoro-1-phenylethyl group.</p>
638	 <p>Chemical structure of compound 638. It is identical to compound 637, featuring a 1,3-dioxane ring system with a 2-pyridylmethyl group, a cyclopentane ring fused to an amide, and a side chain with a 4-phenyl group substituted with a 2-chlorophenyl group and a 2,2-difluoro-1-phenylethyl group.</p>

FIG. 12-252

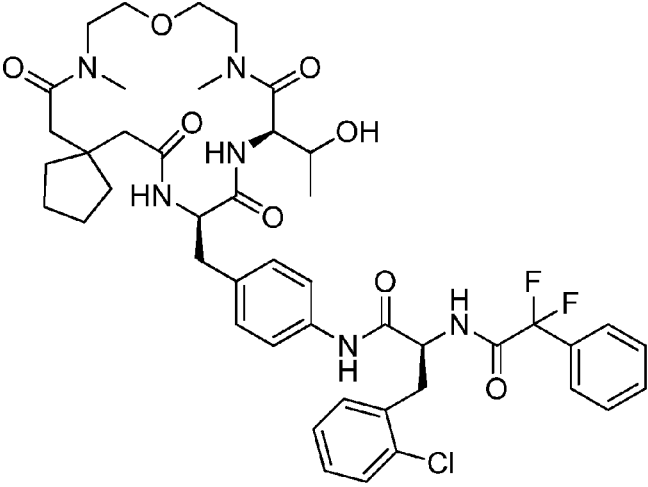
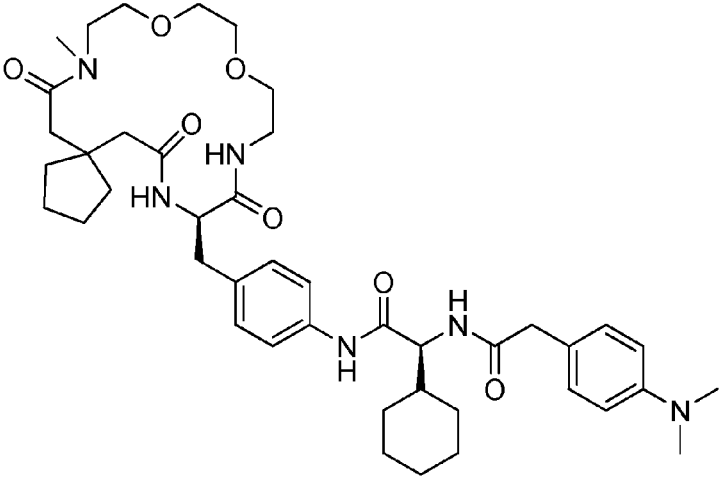
Compound No.	Structure
639	 <p>Chemical structure of Compound 639: A complex molecule featuring a 1,3-dioxane ring system. The 1,3-dioxane ring is substituted with a cyclopentyl group and a carbonyl group. The carbonyl group is part of a chain that includes a secondary amide (HN) and a tertiary amide (N). The tertiary amide is further substituted with a 4-(2-chlorophenyl)phenyl group and a 2-(2,2-difluorophenyl)ethyl group. The secondary amide is substituted with a 2-hydroxypropyl group.</p>
640	 <p>Chemical structure of Compound 640: A complex molecule featuring a 1,3-dioxane ring system. The 1,3-dioxane ring is substituted with a cyclopentyl group and a carbonyl group. The carbonyl group is part of a chain that includes a secondary amide (HN) and a tertiary amide (N). The tertiary amide is further substituted with a 4-(2-(dimethylamino)phenyl)phenyl group and a 2-(cyclohexyl)ethyl group. The secondary amide is substituted with a 2-(dimethylamino)ethyl group.</p>

FIG. 12-253

[illegible]

FIG. 12-254

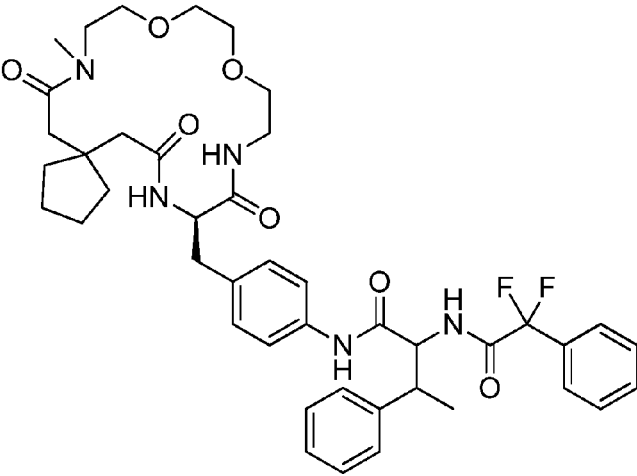
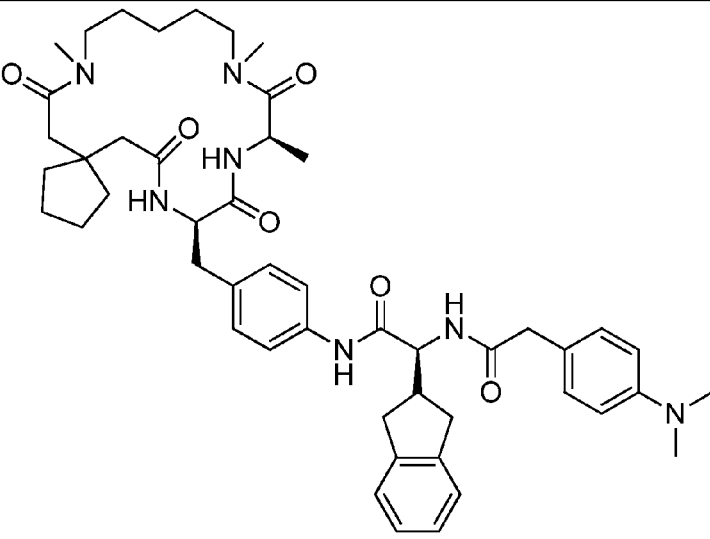
Compound No.	Structure
643	 <p>Chemical structure of Compound 643. It features a 1,3-dioxane ring system fused to a cyclopentane ring. The dioxane ring has a methyl group on one nitrogen and a carbonyl group on the other. A side chain extends from the cyclopentane ring, containing an amide linkage to a chiral center. This chiral center is further substituted with a benzyl group and a side chain that includes a benzamide moiety and a 1,1-difluoro-2-phenylethan-1-yl group.</p>
644	 <p>Chemical structure of Compound 644. It features a 1,3-dioxane ring system fused to a cyclopentane ring. The dioxane ring has a methyl group on one nitrogen and a carbonyl group on the other. A side chain extends from the cyclopentane ring, containing an amide linkage to a chiral center. This chiral center is further substituted with a benzyl group and a side chain that includes a benzamide moiety and a 1-(dimethylaminomethyl)-2-phenylethan-1-yl group.</p>

FIG. 12-255

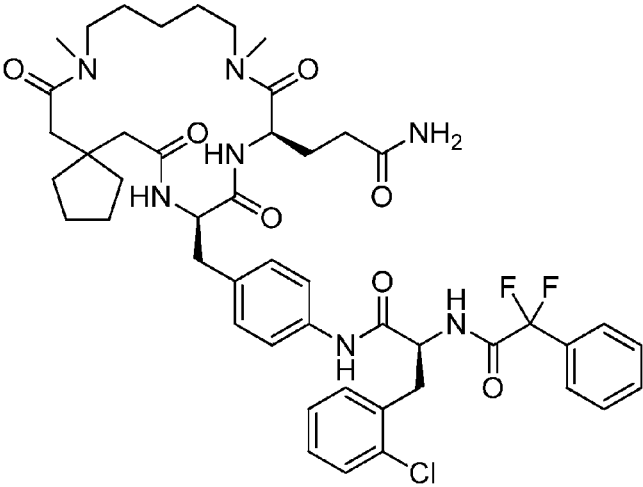
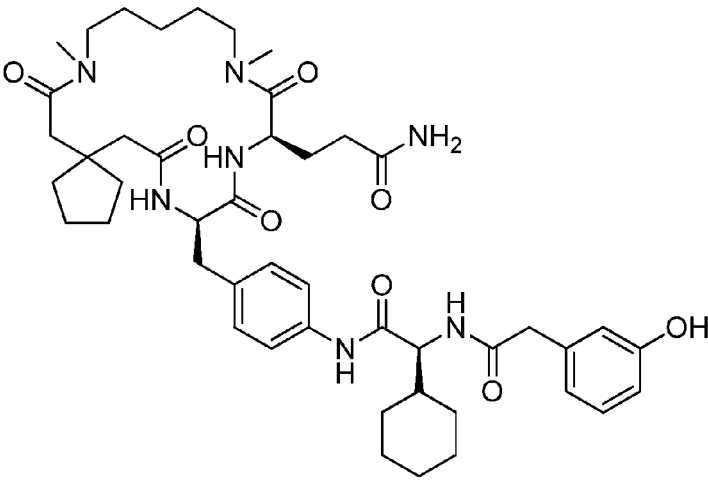
Compound No.	Structure
645	 <p>Chemical structure of Compound 645: A complex molecule featuring a macrocyclic amide ring (12-membered) with two methyl groups on the nitrogen atoms. The macrocycle is linked via amide bonds to a cyclopentyl group and a side chain containing a benzamide moiety. The benzamide is further substituted with a 2-chlorophenyl group and a side chain ending in a 2,2-difluoro-1-phenylethan-1-yl group.</p>
646	 <p>Chemical structure of Compound 646: A complex molecule featuring a macrocyclic amide ring (12-membered) with two methyl groups on the nitrogen atoms. The macrocycle is linked via amide bonds to a cyclopentyl group and a side chain containing a benzamide moiety. The benzamide is further substituted with a cyclohexyl group and a side chain ending in a 4-hydroxyphenyl group.</p>

FIG. 12-256

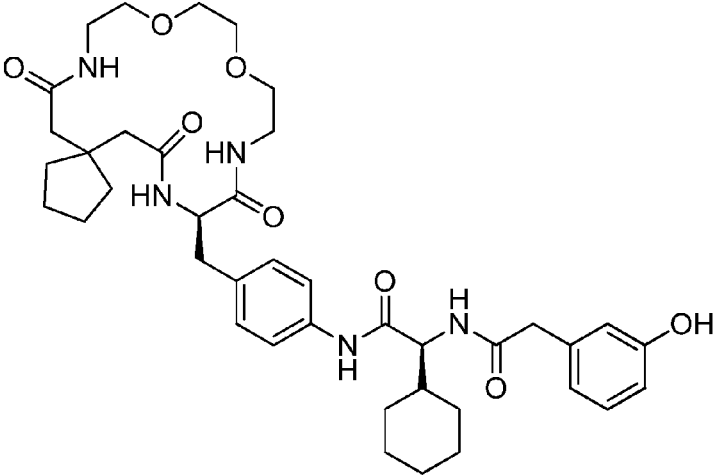
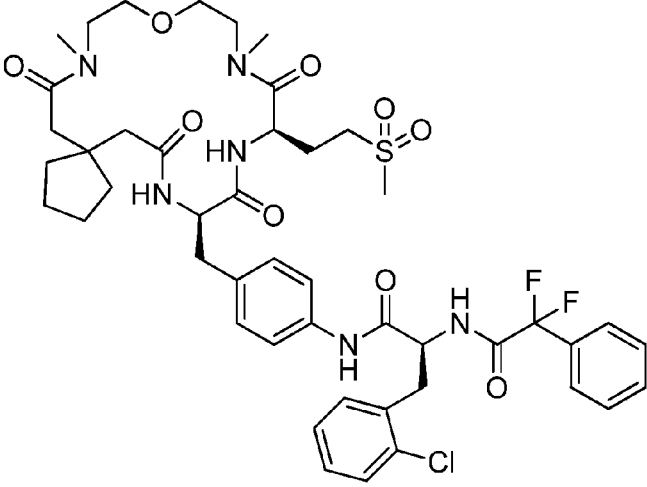
Compound No.	Structure
647	 <p>Chemical structure of Compound 647: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a five-membered ring containing an amide). This is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a cyclohexyl group and an amide linkage to a 4-hydroxyphenyl group.</p>
649	 <p>Chemical structure of Compound 649: A complex molecule featuring a bicyclic amide system (cyclopentane fused to a five-membered ring containing an amide). This is linked via a chiral center to a benzamide moiety, which is further connected to a chiral center bearing a 2-chlorophenyl group and an amide linkage to a 1,1-difluoro-2-phenylethyl group. A sulfonamide group is also present on the side chain.</p>

FIG. 12-257

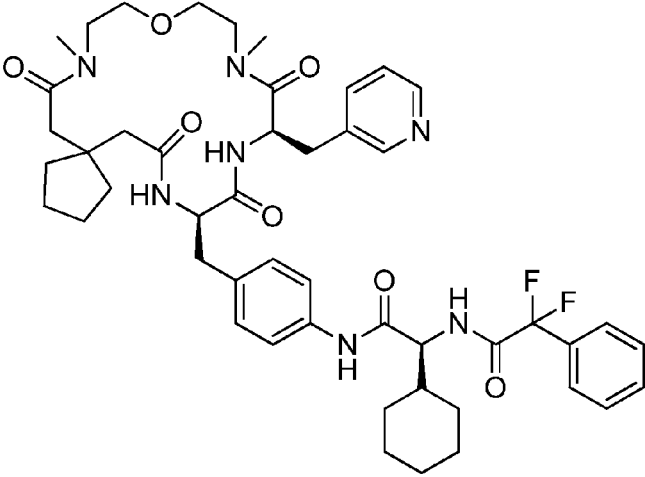
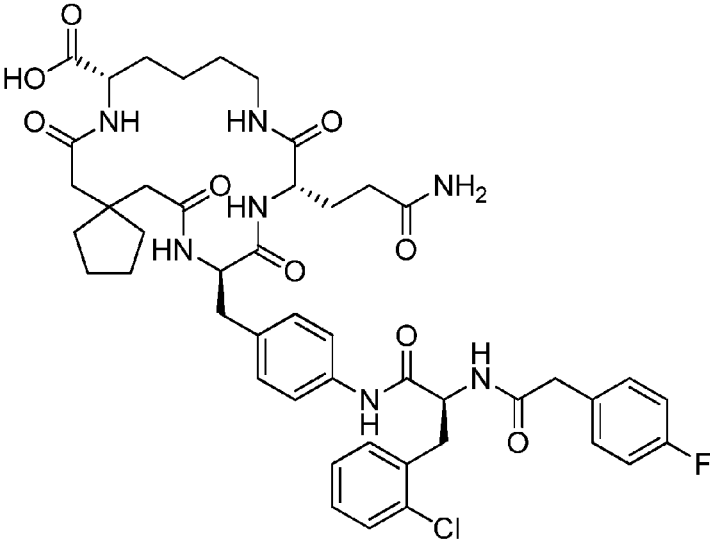
Compound No.	Structure
650	 <p>Chemical structure of Compound 650: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a five-membered ring containing two nitrogen atoms, one of which is a tertiary amine. Another carbon of the cyclopentane is attached to a side chain containing two amide groups. One amide is linked to a pyridine ring, and the other is linked to a side chain containing a benzene ring, a cyclohexane ring, and a difluoromethyl group.</p>
651	 <p>Chemical structure of Compound 651: A complex molecule featuring a central cyclopentane ring. One carbon of the cyclopentane is part of a five-membered ring containing two nitrogen atoms, one of which is a tertiary amine. Another carbon of the cyclopentane is attached to a side chain containing two amide groups. One amide is linked to a side chain containing a carboxylic acid group and a long alkyl chain. The other amide is linked to a side chain containing a benzene ring, a chlorine atom, and a side chain with a fluorine atom.</p>

FIG. 12-258

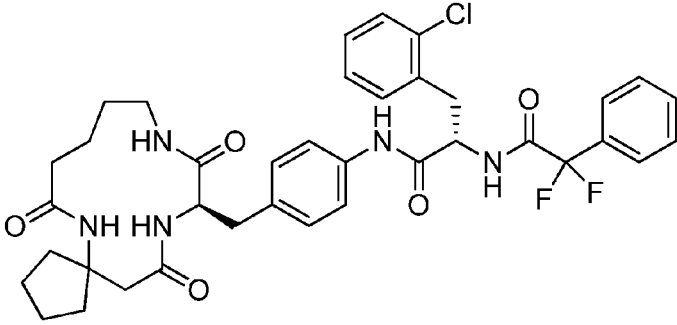
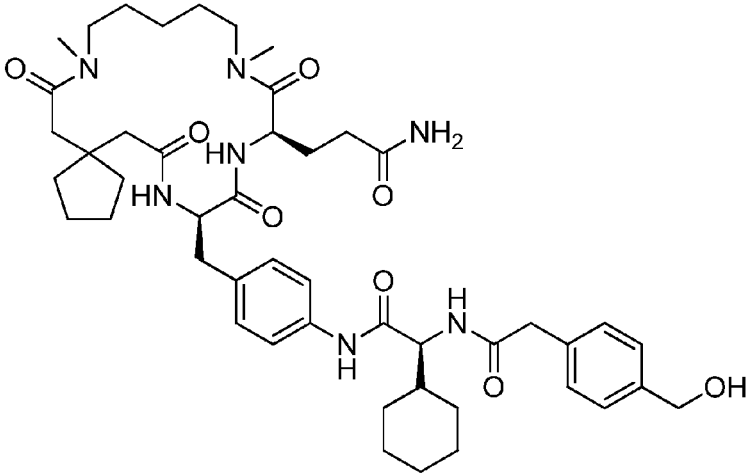
Compound No.	Structure
652	 <p>Chemical structure of Compound 652: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a nitrogen atom. This nitrogen is part of a chain containing a benzimidazole-like system, a benzene ring, and a side chain with a chlorine-substituted benzene ring, a carbonyl group, and a difluoromethyl group.</p>
653	 <p>Chemical structure of Compound 653: A complex molecule featuring a cyclopentane ring substituted with a carbonyl group and a nitrogen atom. This nitrogen is part of a chain containing a benzimidazole-like system, a benzene ring, and a side chain with a carbonyl group, a cyclohexane ring, and a hydroxymethyl group.</p>

FIG. 12-259

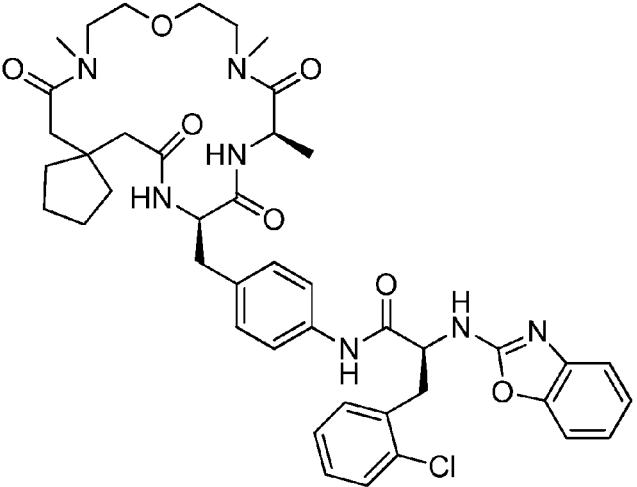
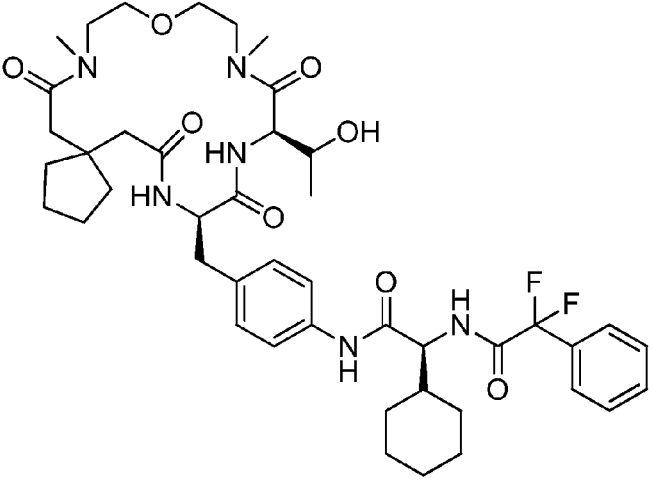
Compound No.	Structure
654	 <p>Chemical structure of Compound 654. It features a macrocyclic core with two N-methyl-N-(cyclopentylmethyl)carbamoyl groups and a central amide linkage. The structure is substituted with a 4-(2-chlorophenyl)phenyl group and a 1H-benzotriazol-4-yl group.</p>
655	 <p>Chemical structure of Compound 655. It features a macrocyclic core with two N-methyl-N-(cyclopentylmethyl)carbamoyl groups and a central amide linkage. The structure is substituted with a 4-(2-fluorophenyl)phenyl group and a 1H-benzotriazol-4-yl group.</p>

FIG. 12-260

Compound No.	Structure
656	
657	

FIG. 12-261

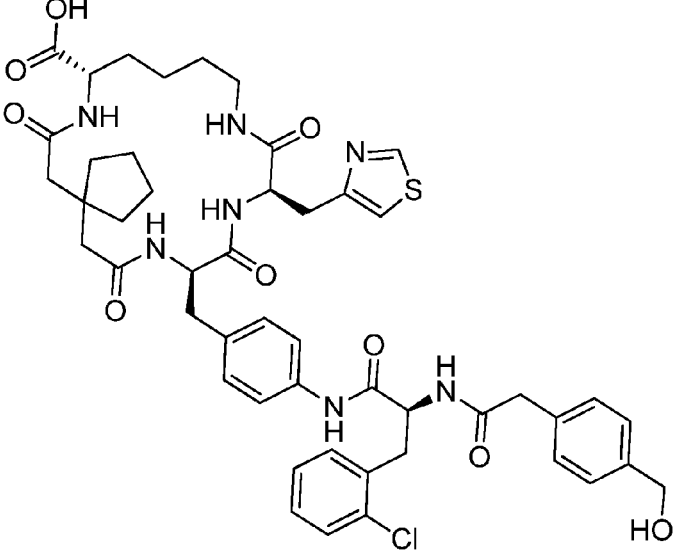
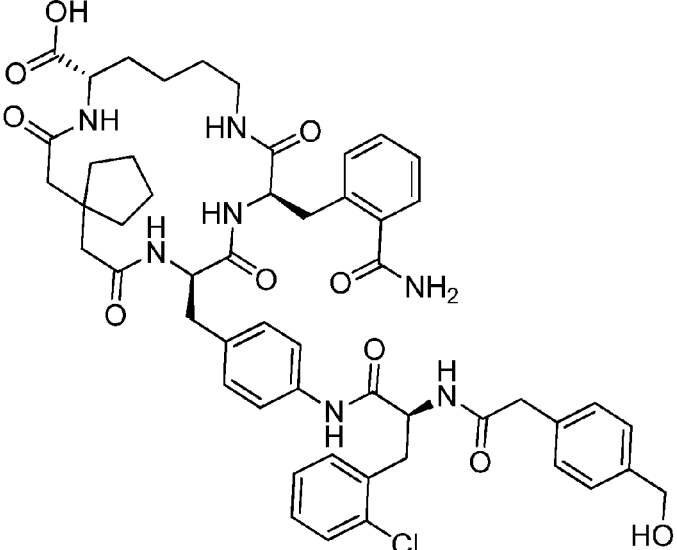
Compound No.	Structure
658	 <p>Chemical structure of compound 658. It features a central benzene ring substituted with a 4-chlorophenyl group, a 4-(hydroxymethyl)phenyl group, and a 4-(hydroxymethyl)phenyl group. The structure includes a complex amide linkage system, a cyclopentyl ring, and a thiazole ring.</p>
659	 <p>Chemical structure of compound 659. It features a central benzene ring substituted with a 4-chlorophenyl group, a 4-(hydroxymethyl)phenyl group, and a 4-(hydroxymethyl)phenyl group. The structure includes a complex amide linkage system, a cyclopentyl ring, and an amide group.</p>

FIG. 12-262

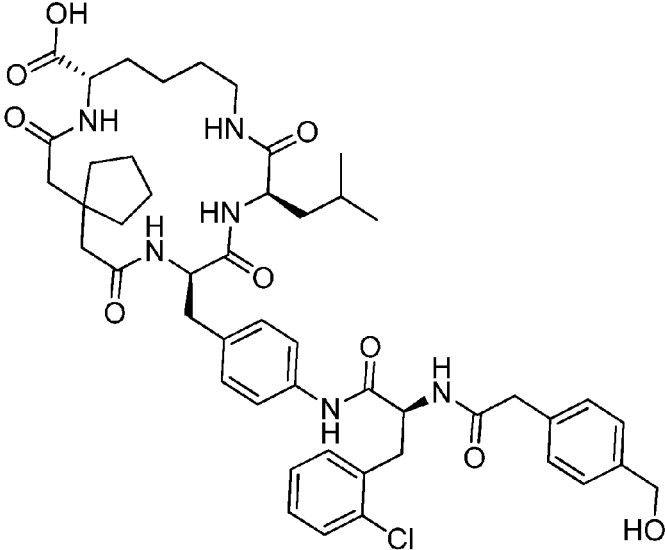
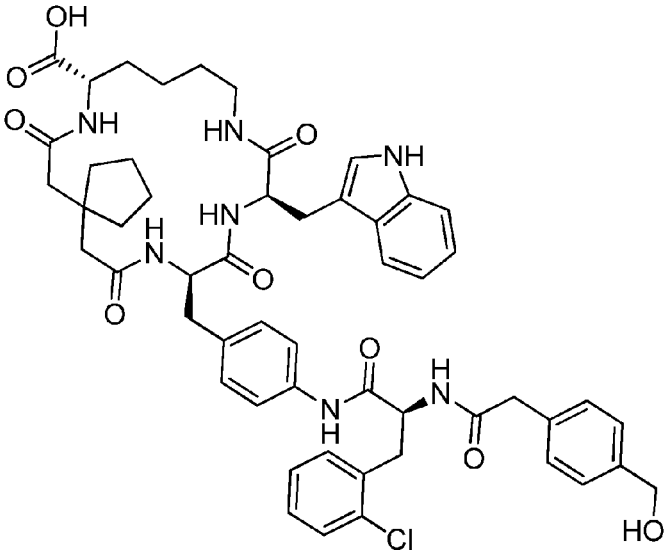
Compound No.	Structure
660	 <p>Chemical structure of Compound 660. It features a cyclopentane ring substituted with a carboxylic acid group (HO-C=O), an amide group (-NH-C(=O)-), and a side chain containing a benzamide moiety. The benzamide is further substituted with a 2-chlorophenyl group and a 4-hydroxybenzyl group. The side chain also includes an amide linkage to a 2-chlorophenyl group and a 4-hydroxybenzyl group.</p>
661	 <p>Chemical structure of Compound 661. It is similar to Compound 660, but the side chain is substituted with an indol-3-ylmethyl group instead of the 2-chlorophenyl group. The rest of the structure, including the cyclopentane ring and the 4-hydroxybenzyl group, remains the same.</p>

FIG. 12-263

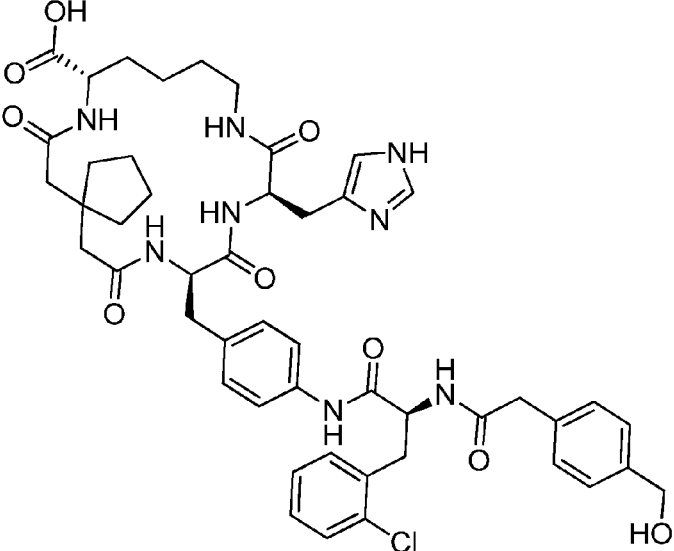
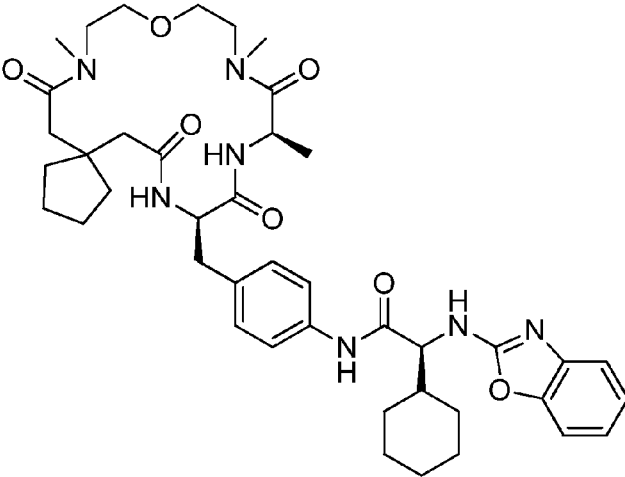
Compound No.	Structure
662	 <p>Chemical structure of Compound 662: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and an amide linkage (-NH-C(=O)-). This amide is connected to a chain containing a pyrazole ring, a benzamide group (-NH-C(=O)-C₆H₄-), and a 2-chlorophenyl group. The structure also includes a hydroxymethyl group (-CH₂OH) and a hydroxyl group (-OH).</p>
663	 <p>Chemical structure of Compound 663: A complex molecule featuring a cyclopentane ring substituted with a carboxylic acid group (HO-C(=O)-) and an amide linkage (-NH-C(=O)-). This amide is connected to a chain containing a benzamide group (-NH-C(=O)-C₆H₄-), a cyclohexyl group, and a benzoxazole ring system. The structure also includes a hydroxyl group (-OH) and a hydroxymethyl group (-CH₂OH).</p>

FIG. 12-264

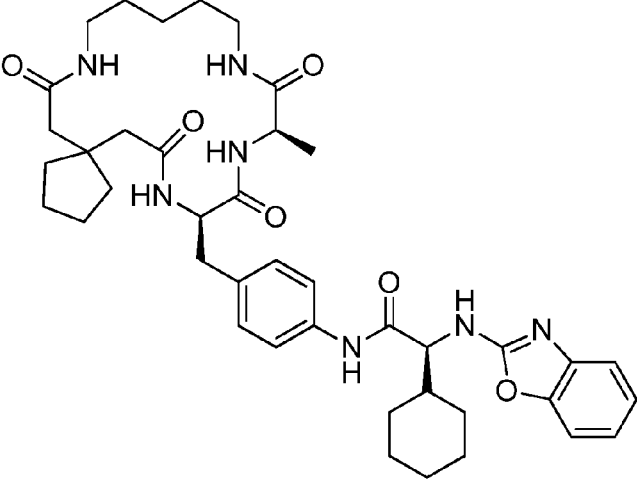
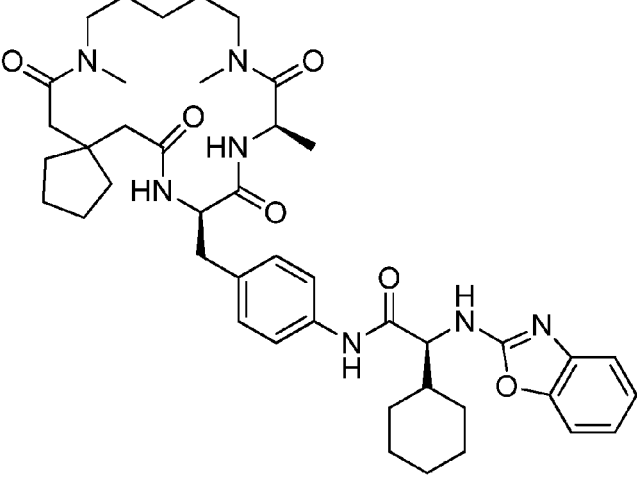
Compound No.	Structure
664	 <p>Chemical structure of compound 664. It features a 1,4-bis(methylamino)hexane-2,5-dione core. The left methylamino group is substituted with a 1-cyclopentyl-2-oxoethyl group. The right methylamino group is substituted with a 1-methyl-2-oxoethyl group. A 4-((1-cyclohexyl-2-oxo-1-((1H-benzotriazol-4-ylideneamino)amino)ethyl)amino)phenyl group is attached to the 1-methyl-2-oxoethyl side chain via its para position.</p>
665	 <p>Chemical structure of compound 665. It is similar to compound 664, but the 1,4-bis(methylamino)hexane-2,5-dione core is replaced by a 1,4-bis(dimethylamino)hexane-2,5-dione core, where both nitrogen atoms are substituted with methyl groups.</p>

FIG. 12-265

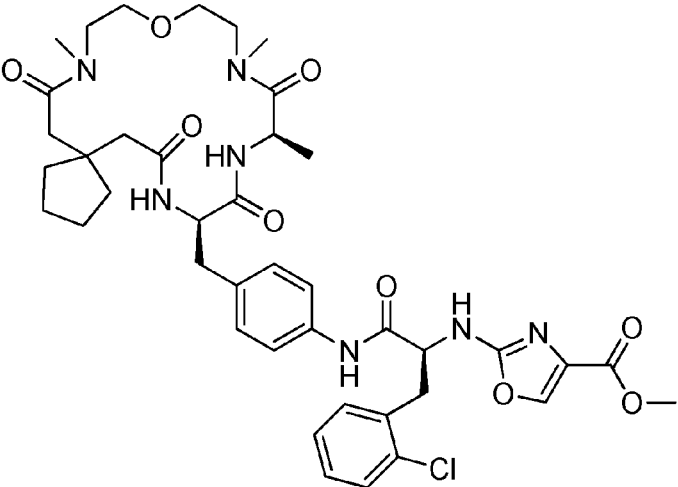
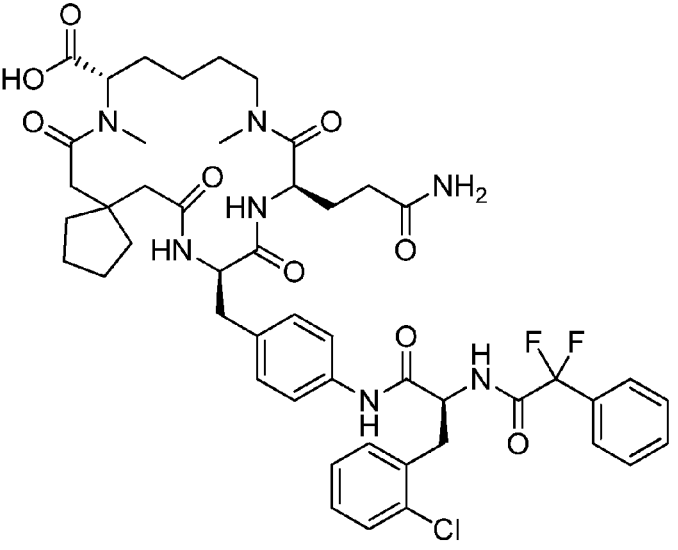
Compound No.	Structure
666	 <p>Chemical structure of Compound 666: A complex molecule featuring a 1,3-dioxane ring system. The 1,3-dioxane ring is substituted with a cyclopentyl group at position 2 and a 4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl group at position 4. The 1,3-dioxane ring is also substituted with a 2-methoxy-5-oxo-1H-imidazol-4-yl group at position 6. The 1,3-dioxane ring is further substituted with a 2-chlorophenyl group at position 5.</p>
667	 <p>Chemical structure of Compound 667: A complex molecule featuring a 1,3-dioxane ring system. The 1,3-dioxane ring is substituted with a cyclopentyl group at position 2 and a 4-(2-chlorophenyl)-2-oxo-1,2,3,4-tetrahydroquinazolin-6-yl group at position 4. The 1,3-dioxane ring is also substituted with a 2-amino-5-oxo-1H-imidazol-4-yl group at position 6. The 1,3-dioxane ring is further substituted with a 2-chlorophenyl group at position 5.</p>

FIG. 12-266

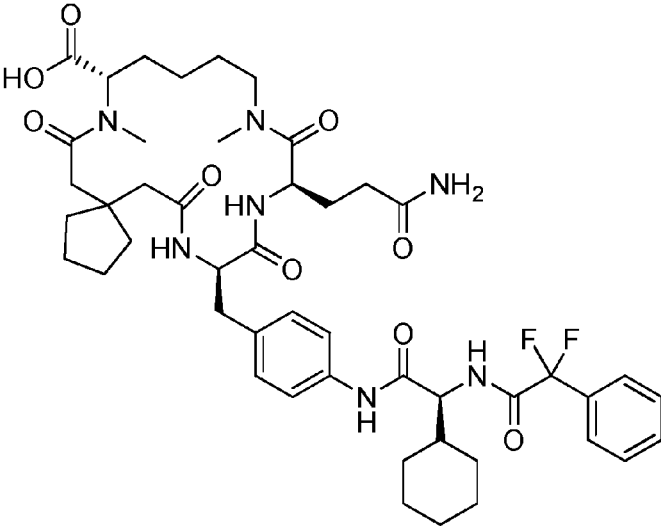
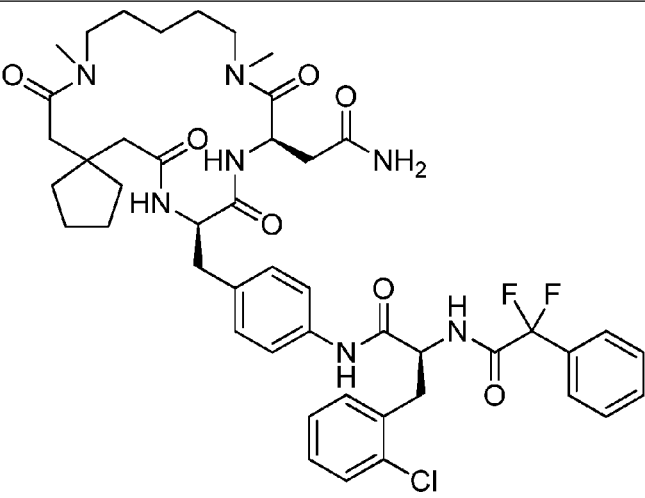
Compound No.	Structure
668	 <p>Chemical structure of Compound 668. It features a macrocyclic core with two methylated nitrogen atoms. A cyclopentyl group is attached to one of the nitrogens. A side chain includes a carboxamide group (NH₂), a secondary amide, and a 4-((2-chloro-1-((2,2-difluoro-1-phenylethyl)amino)-2-oxoethyl)amino)phenyl group. Stereochemistry is indicated with wedges and dashes.</p>
669	 <p>Chemical structure of Compound 669. It is similar to Compound 668 but lacks the cyclopentyl group on the macrocycle. The side chain includes a carboxamide group (NH₂), a secondary amide, and a 4-((2-chloro-1-((2,2-difluoro-1-phenylethyl)amino)-2-oxoethyl)amino)phenyl group. Stereochemistry is indicated with wedges and dashes.</p>

FIG. 12-267

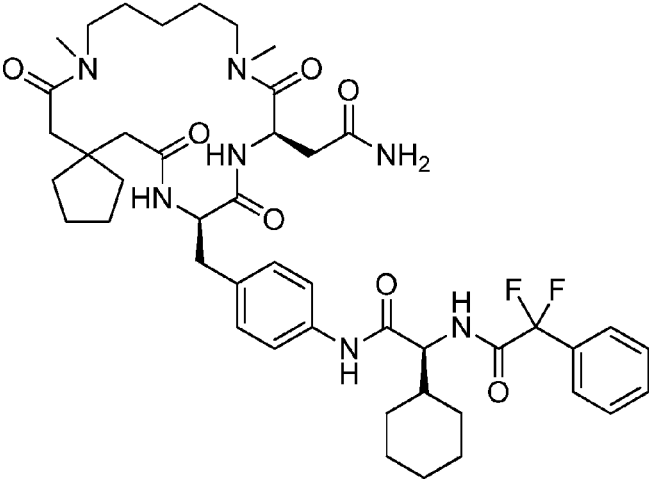
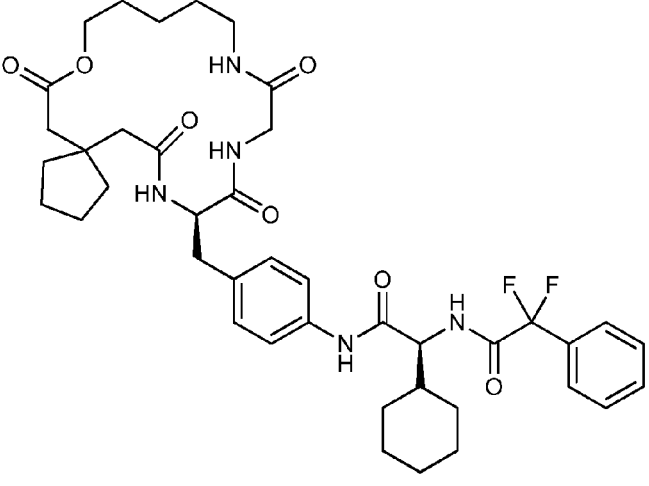
Compound No.	Structure
670	 <p>Chemical structure of Compound 670. It features a cyclopentane ring substituted with a methylcarbamoyl group and a side chain containing two amide bonds. The side chain includes a 4-((1-cyclohexyl-2-((2-aminocarbonylmethyl)amino)propanoyl)amino)phenyl group and a 1-((2-((2-aminocarbonylmethyl)amino)propanoyl)amino)-2,2-difluoro-1-phenylethan-1-yl group.</p>
671	 <p>Chemical structure of Compound 671. It is similar to Compound 670, but the methylcarbamoyl group on the cyclopentane ring is replaced by a methylcarbamate group.</p>

FIG. 12-268

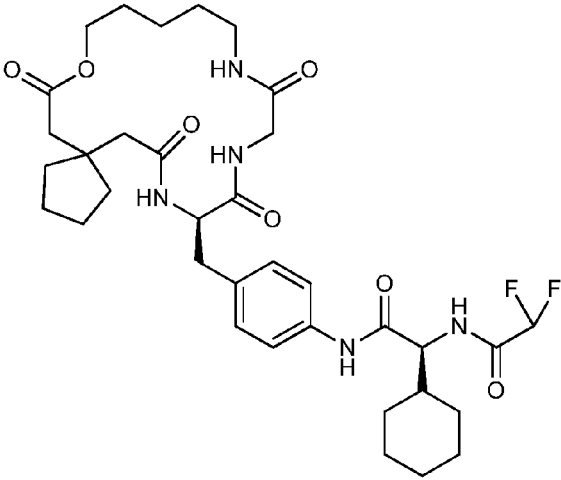
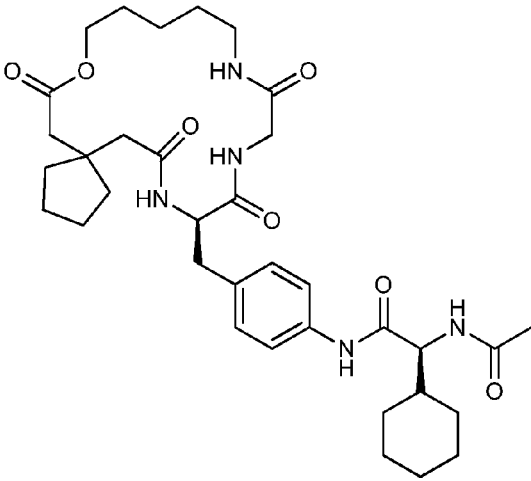
Compound No.	Structure
672	 <p>Chemical structure of compound 672. It features a cyclopentyl group attached to a chain containing two amide bonds and a carbamate group. The chain is further substituted with a benzamide group and a cyclohexyl group, and ends with a trifluoromethyl group.</p>
673	 <p>Chemical structure of compound 673. It features a cyclopentyl group attached to a chain containing two amide bonds and a carbamate group. The chain is further substituted with a benzamide group and a cyclohexyl group, and ends with an acetyl group.</p>

FIG. 12-269

Compound No.	Structure
674	
675	

FIG. 12-270

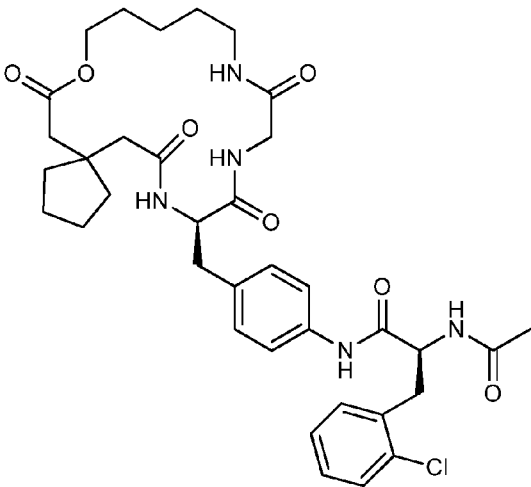
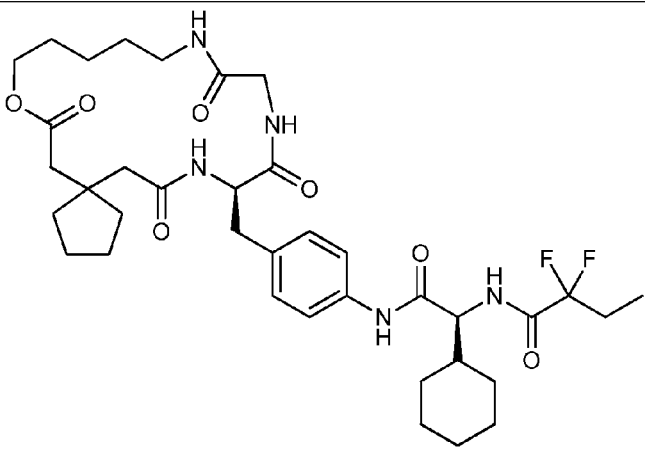
Compound No.	Structure
676	 <p>Chemical structure of Compound 676: A complex molecule featuring a cyclopentyl group attached to a chain containing multiple amide and ester linkages. The structure includes a 4-phenyl group, a 2-chlorophenyl group, and a terminal amide group.</p>
677	 <p>Chemical structure of Compound 677: A complex molecule featuring a cyclopentyl group attached to a chain containing multiple amide and ester linkages. The structure includes a 4-phenyl group, a cyclohexyl group, and a terminal amide group with a fluorinated side chain.</p>

FIG. 12-271

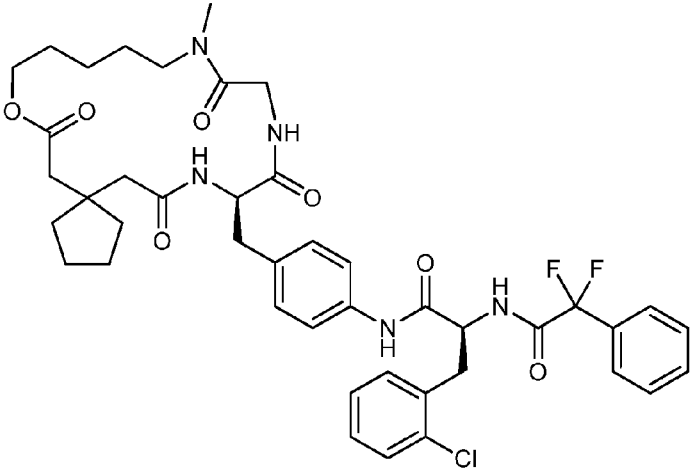
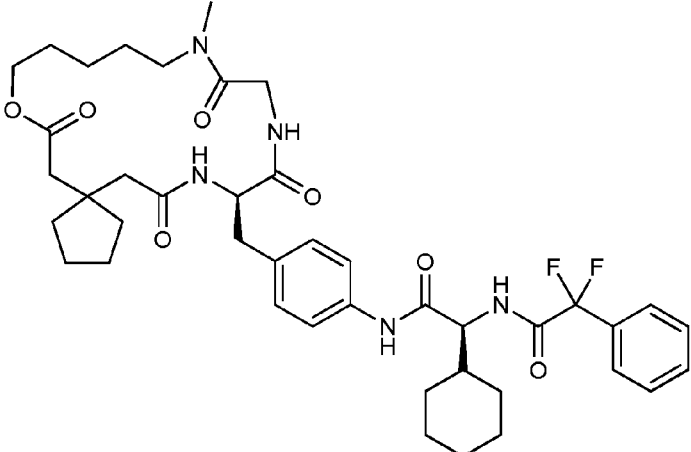
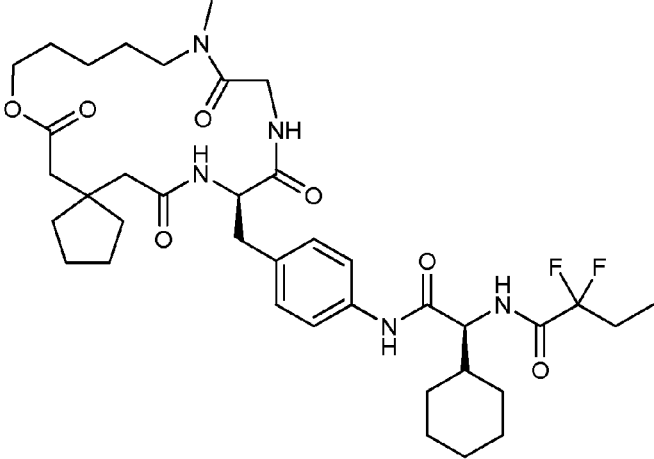
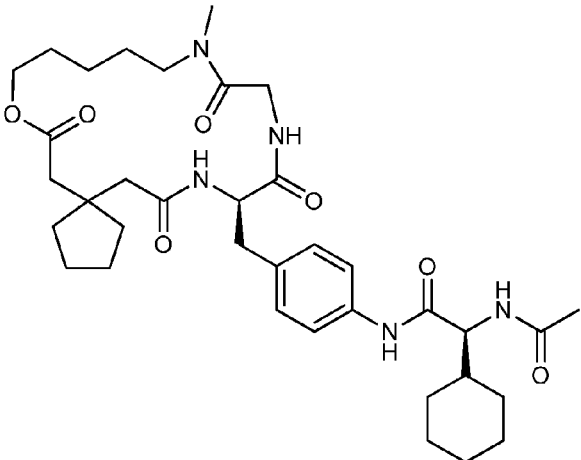
Compound No.	Structure
678	 <p>Chemical structure of compound 678. It features a complex molecule with a central amide linkage. The left side includes a cyclopentyl ring connected to a chain containing a carbonyl group and a methoxy group. The right side includes a benzene ring with a chlorine substituent, connected to a chain containing a carbonyl group and a difluoromethyl group. The structure is highly branched and contains multiple amide and carbonyl functional groups.</p>
679	 <p>Chemical structure of compound 679. It is similar to compound 678 but lacks the chlorine substituent on the benzene ring. The structure is highly branched and contains multiple amide and carbonyl functional groups.</p>

FIG. 12-272

Compound No.	Structure
680	 <p>Chemical structure of Compound 680: A complex molecule featuring a cyclopentyl ring connected to a carbonyl group, which is linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a benzene ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide.</p>
681	 <p>Chemical structure of Compound 681: A complex molecule featuring a cyclopentyl ring connected to a carbonyl group, which is linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a benzene ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide. The tertiary amide is connected to a cyclohexyl ring, which is further linked to a chain containing a secondary amide and a tertiary amide.</p>

MACROCYCLIC COMPOUNDS FOR MODULATING IL-17

CROSS REFERENCE TO RELATED APPLICATIONS

This application is the national stage of International (PCT) Patent Application serial number PCT/US2013/024386, filed Feb. 1, 2013, which claims the benefit of and priority to U.S. Provisional Patent Application Ser. No. 61/593,993, filed Feb. 2, 2012, and U.S. Provisional Patent Application Ser. No. 61/725,878, filed Nov. 13, 2012, the contents of each of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The invention relates generally to macrocyclic compounds and their therapeutic use. More particularly, the invention relates to macrocyclic compounds that modulate the activity of IL-17 and/or are useful in the treatment of medical conditions, such as inflammatory diseases and other IL-17-associated disorders.

BACKGROUND OF THE INVENTION

Interleukin-17 ("IL-17"), also known as IL-17A and CTLA-8, is a pro-inflammatory cytokine that stimulates secretion of various other cytokines in a variety of cell types. For example, IL-17 can induce IL-6, IL-8, G-CSF, TNF- α , IL-1 β , PGE2, and IFN- γ , as well as numerous chemokines and other effectors. See, e.g., Gaffen, S L, *Arthritis Research & Therapy* 6: 240-247 (2004).

IL-17 is expressed by TH17 cells, which are involved in the pathology of inflammation and autoimmunity. It is also expressed by CD8+ T cells, $\gamma\delta$ cells, NK cells, NKT cells, macrophages and dendritic cells. IL-17 and Th17 are linked to pathogenesis of diverse autoimmune and inflammatory diseases, but are essential to host defense against many microbes, particularly extracellular bacteria and fungi. Human IL-17A is a glycoprotein with a molecular weight of 17,000 daltons (Spriggs et al., *J Clin Immunol*, 17: 366-369 (1997)). IL-17 can form homodimers or heterodimers with its family member, IL-17F. IL-17 binds to both IL-17 RA and IL-17 RC to mediate signaling. IL-17, signaling through its receptor, activates the NF- κ B transcription factor, as well as various MAPKs. See, e.g., Gaffen, S L, *Nature Rev Immunol*, 9: 556-567 (2009).

IL-17 can act in cooperation with other inflammatory cytokines such as TNF- α , IFN- γ , and IL-1 β to mediate pro-inflammatory effects. See, e.g., Gaffen, S L, *Arthritis Research & Therapy* 6: 240-247 (2004); US Publication No 20080269467 A1, published Oct. 30, 2008. IL-17 was found in higher serum concentrations in patients with systemic lupus erythematosus (SLE) and was recently determined to act either alone or in synergy with B-cell activating factor (BAFF) to control B-cell survival, proliferation, and differentiation into immunoglobulin producing cells. Doreau et al., *Nature Immunology* 7:778-785 (2009). IL-17 has also been associated with ocular surface disorders, such as dry eye (PCT publication WO2010062858 and WO2011163452). IL-17 has also been

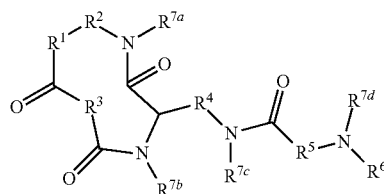
implicated in playing a role in ankylosing spondylitis (H. Appel et al., *Arthritis Research and Therapy* 2011, 13R95) and psoriatic arthritis (McInnes, I. et al. *Arthritis & Rheumatism*, 2011; Volume 63, Suppl. 10:779).

IL-17 and IL-17-producing TH17 cells have recently been implicated in certain cancers, Ji and Zhang, *Cancer Immunol Immunother* 59: 979-987 (2010). For example, IL-17-expressing TH17 cells were shown to be involved in multiple myeloma, Prabhala et al., *Blood*, online DOI 10.1182/blood-2009-10-246660, Apr. 15, 2010, and to correlate with poor prognosis in patients with hepatocellular carcinoma (HCC), Zhang et al., *J Hepatology* 50: 980-89 (2009). Also, IL-17 was found to be expressed by breast-cancer-associated macrophages, Zhu et al., *Breast Cancer Research* 10:R95 (2008). However, the role of IL-17 in cancer, in many cases, has been unclear. In particular, IL-17 and IL-17-producing TH17 cells have been identified as having both a positive and a negative role in tumor immunity, sometimes in the same type of cancer. For a review, see, Ji and Zhang, *Cancer Immunol Immunother* 59: 979-987 (2010).

It can be seen from above that modulation of IL-17 has important therapeutic implications. Although various antibodies to IL-17 have been described in the prior art, very few small molecule-type, specific modulators of IL-17 with oral bioavailability are known. Accordingly, there is a need for the development of small molecule-like modulators of IL-17.

SUMMARY

The present invention provides macrocyclic compounds, methods of modulating the activity of IL-17, and methods for treating various medical conditions using such compounds. In one aspect, the invention provides a compound represented by Formula I:



including pharmaceutically acceptable salts thereof, wherein the variables are as defined in the detailed description.

In another aspect, the invention provides a method of treating a patient suffering from or susceptible to a medical condition that is mediated directly or indirectly by IL-17. A number of medical conditions can be treated. The method comprises administering to the patient a therapeutically effective amount of a composition comprising a macrocyclic compound described herein. For example, the compounds described herein may be used to treat or prevent inflammatory diseases and conditions, proliferative diseases (e.g., cancer), autoimmune diseases and other disease described herein.

In another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of IL-17; and b) if the patient does have an elevated level of IL-17, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition.

In still another aspect, the invention provides a method of treating a patient suffering from a disease or condition asso-

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ciated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of one or more IL-17-induced chemokine or effector; and b) if the patient does have an elevated level of the one or more IL-17 chemokine or effector, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition. In certain aspects, the IL-17 chemokine or effector is one or more of IL-6, IL-8, G-CSF, TNF- α , IL-1 β , PGE2, and IFN- γ .

The foregoing and other aspects and embodiments of the invention may be more fully understood by reference to the following detailed description and claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts the effect of two intraperitoneally dosed exemplary compounds of the invention (i.e., compound nos. 159 and 181) on edema, TNF- α , and IFN- γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and vehicle controls.

FIG. 2 depicts the dose-dependent effect of an intraperitoneally dosed exemplary compound of the invention (i.e., compound 159) on edema, IL-6, and IFN- γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and a vehicle control.

FIG. 3 depicts the dose-dependent effect of an orally dosed exemplary compound of the invention on edema, IL-6, and IFN- γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and a vehicle control.

FIG. 4 depicts the effect of an orally dosed exemplary compound of the invention on edema, IL-6, IFN- γ and CXCL-1 in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. 5 depicts the dose-dependent effect of an orally dosed exemplary compound of the invention on edema, IL-6, and IFN- γ in a murine delayed hypersensitivity assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. 6 depicts the effect over time on all paws of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and various vehicle controls.

FIG. 7 depicts the effect on all paws of an orally dosed exemplary compound of the invention on Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. 8 depicts the effect on all joints of an orally dosed exemplary compound of the invention on various pathological parameters in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. 9 depicts the sum effect of an orally dosed exemplary compound of the invention on measured pathological parameters in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and a vehicle control.

FIG. 10 depicts the effect over time on all paws of two different dosages of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and vehicle controls.

FIG. 11 depicts the overall effect on all paws of two different dosages of an orally dosed exemplary compound of the invention on Mean Clinical Arthritis Score in a murine collagen-induced arthritis ("CIA") assay, as compared to an IL-17 antibody and vehicle controls.

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FIG. 12 is a table of exemplary compounds of the invention (Table 1).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides macrocyclic compounds, methods of modulating the activity of IL-17, and methods for treating various medical conditions, especially inflammatory conditions and diseases, using such compounds. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, and biochemistry. For example, procedures for synthesizing organic compounds are described in the literature, such as "Comprehensive Organic Synthesis" (BM Trost & I Fleming, eds., 1991-1992). Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section. Further, when a variable is not accompanied by a definition, the previous definition of the variable controls.

I. DEFINITIONS

To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

The term "alkyl" is art-recognized and refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as C₁-C₁₂ alkyl, C₁-C₁₀ alkyl, and C₁-C₆ alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

The terms "alkenyl" and "alkynyl" are art-recognized and refer to unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond, respectively.

The term "cycloalkyl" is art-recognized and refers to a monovalent fully saturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-10, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as "C₄₋₈ cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexane, cyclopentane, cyclobutane, and cyclopropane.

The term "alkylene" refers to the diradical of an alkyl group.

The term "C₀ alkylene" as used herein means a bond. Thus, a moiety defined herein as "(C₀-C₆ alkylene)-aryl" includes both -aryl (i.e., C₀ alkylene-aryl) and -(C₁-C₆ alkylene)-aryl.

The terms "alkenylene" and "alkynylene" refer to the diradicals of an alkenyl and an alkynyl group, respectively.

The term "methylene unit" refers to a divalent —CH₂— group present in an alkyl or alkylene moiety.

The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. For example, —CH₂F, —CHF₂, —CF₃, —CH₂CF₃, —CF₂CF₃, and the like.

The term "carbocyclyl", as used herein, means a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein each ring is either completely saturated or contains one or more units of unsaturation, but where no ring is aromatic. Representative carbocyclyl groups include cycloalkyl groups (e.g., cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and

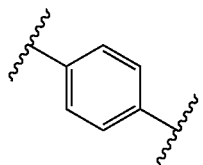
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the like), and cycloalkenyl groups (e.g., cyclopentenyl, cyclohexenyl, cyclopentadienyl, and the like).

The term "aryl" is art-recognized and refers to a monocyclic, bicyclic or polycyclic hydrocarbon ring system, wherein at least one ring is aromatic. Representative aryl groups include fully aromatic ring systems, such as phenyl, naphthyl, and anthracenyl, and ring systems where an aromatic carbon ring is fused to one or more non-aromatic carbon rings, such as indanyl, phthalimidyl, naphthimidyl, or tetrahydronaphthyl, and the like.

The term "arylene" refers to the diradical of an aryl group.

The term "1,4-phenylene" refers to a diradical of phenyl having the formula:



wherein each "w" represents a connection to the rest of the compound.

The term "heteroaryl" is art-recognized and refers to monocyclic, bicyclic or polycyclic ring system wherein at least one ring is both aromatic and comprises a heteroatom; and wherein no other rings are heterocyclyl (as defined below). In certain instances, a ring which is aromatic and comprises a heteroatom contains 1, 2, 3, or 4 ring heteroatoms in such ring. Representative heteroaryl groups include ring systems where (i) each ring comprises a heteroatom and is aromatic, e.g., imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrrolyl, furanyl, thiophenyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl; (ii) each ring is aromatic or carbocyclyl, at least one aromatic ring comprises a heteroatom and at least one other ring is a hydrocarbon ring or e.g., indolyl, isoindolyl, benzothieryl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, pyrido[2,3-b]-1,4-oxazin-3(4H)-one, 5,6,7,8-tetrahydroquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl; and (iii) each ring is aromatic or carbocyclyl, and at least one aromatic ring shares a bridgehead heteroatom with another aromatic ring, e.g., 4H-quinolizinyl.

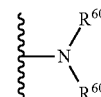
The term "heterocyclyl" refers to monocyclic, bicyclic and polycyclic ring systems where at least one ring is saturated or partially unsaturated (but not aromatic) and comprises a heteroatom. A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Representative heterocyclyls include ring systems in which (i) every ring is non-aromatic and at least one ring comprises a heteroatom, e.g., tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxaninyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl; (ii) at least one ring is non-aromatic and comprises a heteroatom and at least one other ring is an aromatic carbon ring, e.g., 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl; and (iii) at least one ring is non-aromatic and comprises a heteroatom and at least

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one other ring is aromatic and comprises a heteroatom, e.g., 3,4-dihydro-1H-pyrano[4,3-c]pyridine, and 1,2,3,4-tetrahydro-2,6-naphthyridine.

The term "saturated heterocyclyl" refers to a heterocyclyl wherein every ring is saturated, e.g., tetrahydrofuran, tetrahydro-2H-pyran, pyrrolidine, piperidine and piperazine.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formula:



wherein each R⁶⁰ independently represent hydrogen or alkyl.

The terms "alkoxy" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxy groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. The term "alkenyloxy" is art-recognized and refers to an alkenyl group, as defined above, having an oxygen radical attached thereto.

In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at each position. Combinations of substituents envisioned under this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group (such as an alkyl, alkenyl, alkynyl, alkylene, alkenylene, alkynylene or the carbon atom of a carbocyclyl, aryl, heterocyclyl or heteroaryl) are independently halogen; $-(CH_2)_{0-4}R^{\circ}$; $-(CH_2)_{0-4}OR^{\circ}$; $-O-(CH_2)_{0-4}C(O)OR^{\circ}$; $-(CH_2)_{0-4}CH(OR^{\circ})_2$; $-(CH_2)_{0-4}SR^{\circ}$; $-(CH_2)_{0-4}Ph$, which may be substituted with R[°]; $-(CH_2)_{0-4}O(CH_2)_{0-4}Ph$ which may be substituted with R[°]; $-CH=CHPh$, which may be substituted with R[°]; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^{\circ})_2$; $-(CH_2)_{0-4}N(R^{\circ})C(O)R^{\circ}$; $-N(R^{\circ}C(S)R^{\circ})$; $-(CH_2)_{0-4}N(R^{\circ})C(O)NR_2^{\circ}$; $-N(R^{\circ})C(S)NR_2^{\circ}$; $-(CH_2)_{0-4}N(R^{\circ})C(O)OR^{\circ}$; $-N(R^{\circ})N(R^{\circ}C(O)R^{\circ})$; $-N(R^{\circ})N(R^{\circ})C(O)NR_2^{\circ}$; $-N(R^{\circ})N(R^{\circ}C(O)OR^{\circ})$; $-(CH_2)_{0-4}C(O)R^{\circ}$; $-C(S)R^{\circ}$; $-(CH_2)_{0-4}C(O)OR^{\circ}$; $-(CH_2)_{0-4}C(O)SR^{\circ}$; $-(CH_2)_{0-4}C(O)OSiR_3^{\circ}$; $-(CH_2)_{0-4}OC(O)R^{\circ}$; $-OC(O)(CH_2)_{0-4}SR^{\circ}$; $SC(S)SR^{\circ}$; $-(CH_2)_{0-4}SC(O)R^{\circ}$; $-(CH_2)_{0-4}C(O)NR_2^{\circ}$; $-C(S)NR_2^{\circ}$; $-C(S)SR^{\circ}$; $-(CH_2)_{0-4}OC(O)NR_2^{\circ}$; $-C(O)N(OR^{\circ})R^{\circ}$; $-C(O)C(O)R^{\circ}$; $-C(O)CH_2C(O)R^{\circ}$; $-C(NOR^{\circ})R^{\circ}$; $-(CH_2)_{0-4}SSR^{\circ}$; $-(CH_2)_{0-4}S(O)_2R^{\circ}$; $-(CH_2)_{0-4}S(O)_2OR^{\circ}$; $-(CH_2)_{0-4}OS(O)_2R^{\circ}$; $-S(O)_2NR_2^{\circ}$; $-(CH_2)_{0-4}S(O)R^{\circ}$; $-N(R^{\circ})S(O)_2NR_2^{\circ}$; $-N(R^{\circ})S(O)_2R^{\circ}$; $-N(OR^{\circ})R^{\circ}$; $-C(NH)NR_2^{\circ}$; $-P(O)_2R^{\circ}$; $-P(O)RO_2$; $-OP(O)RO_2$; $-OP(O)(OR^{\circ})_2$; $-SiR_3^{\circ}$; $-(C_{1-4}$ straight or branched alkylene)-N(R[°])₂; or $-(C_{1-4}$ straight or branched alkylene)

$C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^*$, $-(haloR^*)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^*$, $-(CH_2)_{0-2}CH(OR^*)_2$, $-O(haloR^*)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^*$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^*$, $-(CH_2)_{0-2}SR^*$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^*$, $-(CH_2)_{0-2}NR^*_2$, $-NO_2$, $-SiR^*_3$, $-OSiR^*_3$, $-C(O)SR^*$, $-(C_{1-4} \text{ straight or branched alkylene})C(O)OR^*$, or $-SSR^*$ wherein each R^* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*)_2)_{2-3}O-$, or $-S(C(R^*)_2)_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(C(R^*)_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R^* include halogen, $-R^*$, $-(haloR^*)$, $-OH$, $-OR^*$, $-O(haloR^*)$, $-CN$, $-C(O)OH$, $-C(O)OR^*$, $-NH_2$, $-NHR^*$, $-NR^*_2$, or $-NO_2$, wherein each R^* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$, wherein each R^\dagger is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R^\dagger , taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated,

partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

Suitable substituents on the aliphatic group of R_t are independently halogen, $-R^*$, $-(haloR^*)$, $-OH$, $-OR^*$, $-O(haloR^*)$, $-CN$, $-C(O)OH$, $-C(O)OR^*$, $-NH_2$, $-NHR^*$, $-NR^*_2$, or $-NO_2$, wherein each R^* is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

The term "moiety" refers to a portion of a compound of this invention comprising at least one hydrogen atom and at least one carbon atom.

Certain compounds of the present invention may exist in particular geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivatizing with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound, as well as enantiomeric mixtures thereof.

As used herein, the term "patient" refers to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (e.g., murines, simians, equines, bovines, porcines, canines, felines, and the like), and most preferably includes humans.

As used herein, the term "effective amount" refers to the amount of a compound (e.g., a compound of the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, e.g., lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use in vivo or ex vivo.

As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (e.g., acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from

inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

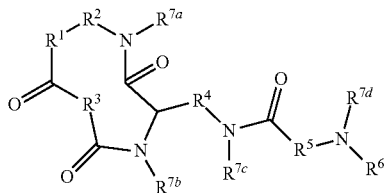
Examples of bases include, but are not limited to, alkali metals (e.g., sodium) hydroxides, alkaline earth metals (e.g., magnesium) hydroxides, ammonia, and compounds of formula NW_4^+ hydroxide, wherein W is C_{1-4} alkyl, and the like.

Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

II. MACROCYCLIC COMPOUNDS

In one aspect, the invention provides a compound represented by Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from $-O-$ and $-N((C_0-C_3 \text{ alkylene})-Q)-$, wherein

Q is selected from hydrogen, $-N(R^{2e})-$, $-OH$, $-O-C_1-C_4$ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

the alkylene portion of R^1 , if present, is optionally substituted; and

when the $-C(O)-$ group adjacent to R^1 is bound directly to an $-N(R^{2h})-$ in R^3 , R^1 is additionally selected from $-CH_2-$;

R^2 is an optionally substituted C_3-C_{12} alkylene, optionally substituted C_3-C_{12} alkenylene, or optionally substituted C_3-C_{12} alkynylene, wherein:

up to three methylene units of R^2 are optionally and independently replaced with $-O-$, $-N(R^c)-$, $-S-$, $-S(O)-$, or $-S(O)_2-$, wherein

R^c is selected from hydrogen, C_1-C_4 alkyl, $-C(O)-C_1-C_3$ alkyl, $-C(O)-(C_1-C_3 \text{ alkylene})$ -aryl, $-C(O)-(C_1-C_3 \text{ alkylene})$ -heteroaryl, $-C(O)-O-C_1-C_3$ alkyl, $-C(O)-O-C_1-C_3$ alkenyl, $-S(O)_2-C_1-C_3$ alkyl, $-S(O)_2-(C_1-C_3 \text{ alkylene})$ -aryl, and $-S(O)_2-(C_1-C_3 \text{ alkylene})$ -heteroaryl; or

when R^1 is $-N((C_0-C_3 \text{ alkylene})-Q)-$, R^c is optionally taken together with R^1 and any intervening atoms to form a heterocyclyl;

any two substituents bound to a common carbon atom in R^2 are optionally taken together to form $=O$, carbocyclyl, or heterocyclyl;

any two substituents bound to different carbon atoms in R^2 are optionally taken together with any intervening atoms to form an aryl, heteroaryl, carbocyclyl, or heterocyclyl;

any two R^c are optionally taken together with the nitrogen atoms to which they are bound and any intervening atoms to form a heterocyclyl; and

any substituent bound to a carbon atom in R^2 is optionally taken together with any one R^c or with R^{7a} and any intervening atoms to form heteroaryl or heterocyclyl;

R^3 is $-[C(R^d)(R^e)]_p-[N(R^{7h})]_{0-1}-[C(R^d)(R^e)]_q-$, wherein:

each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl, or heterocyclyl;

p is 0, 1 or 2;

q is 0, 1 or 2; and

p+q is 2 or more;

R^4 is $-[C(R^e)(R^f)]_n-Y-[C(R^e)(R^f)]_m-$, wherein:

each R^e is independently selected from hydrogen and a suitable alkylene substituent;

Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, and optionally substituted C_1-C_3 alkylene;

each of n and m are independently selected from 0, 1, 2, 3, 4, 5, and 6; and n+m is 6 or less;

R^5 is C_1-C_2 alkylene substituted with one or more $-(C_0-C_5 \text{ alkylene})-R^f$, wherein each R^f is independently selected from $-CH_3$, $-O-C_1-C_3$ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^6 is selected from heteroaryl, $-CH_2$ -aryl, $-C(O)-R^8$, $-C(O)-O-R^8$, $-C(O)-C(O)-R^8$, $-S(O)-R^8$, $-S(O)_2-R^8$, $C(O)-N(R^{2f})-R^8$, and $-S(O)_2-N(R^{2f})-R^8$;

each R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{7f} , and R^{7g} is independently selected from hydrogen and C_1-C_4 alkyl;

R^{7h} is independently selected from hydrogen, C_1-C_4 alkyl, phenyl, and benzyl;

R^8 is selected from $-(C_0-C_6 \text{ alkylene})$ -aryl, $-(C_0-C_6 \text{ alkylene})$ -heteroaryl, $-(C_0-C_6 \text{ alkylene})$ -carbocyclyl, $-(C_0-C_6 \text{ alkylene})$ -heterocyclyl, and C_1-C_6 alkyl, wherein

when R^8 is C_1-C_6 alkyl, up to two methylene units in the alkyl are optionally and independently replaced with $-O-$, $-N(R^{7g})-$, $-S-$, $-S(O)-$, or $-S(O)_2-$; and

any alkyl or alkylene portion of R^8 is optionally substituted with an appropriate alkyl or alkylene substituent other than $=O$; or

R^{7d} and R^6 are optionally taken together to form a heterocyclyl; and

any aryl, heteroaryl, carbocyclyl, or heterocyclyl portion of the compound is optionally substituted.

It will be understood by those of skill in the art that the optional and independent replacement of up to three methyl-

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ene units of R² with —O—, —N(R^c)—, —S—, —S(O)—, or —S(O)₂—, contemplated by the present invention only includes such replacements that result in a stable compound. Accordingly, compounds containing combinations of such replacements that are known to be unstable, e.g., —O—O—, —S(O)—S(O)₂—, —N(R^c)—N(R^c)—O—, and the like, are not to be considered within the scope of the invention. It will be understood by those of skill in the art that because the compounds of the invention are limited to compounds that are stable, compounds formed by the optional and independent replacement of up to three methylene units in R² with certain combinations of —O—, —S—, —S(O)—, —S(O)₂—, or —NR^c— are not within the scope of the present invention. For example, compounds wherein the R² moiety comprises an —O—, —S—, —S(O)—, —S(O)₂—, or —N(R^c)—, adjacent to an —O—, —S—, —S(O)—, —S(O)₂—, or —N(R^c)— are not within the scope of the present invention, except for an —S(O)₂— adjacent a —N(R^c)—. In addition, R² should not comprise —O—CH₂—O—, —N—CH₂—O—, or —O—CH₂—N—, wherein the —CH₂— portion thereof is optionally substituted, except when the —CH₂— portion is substituted to become —C(O)—.

In certain embodiments of Formula I, R¹ is selected from —O— and —N((C₀-C₃ alkylene)-Q)-, wherein Q is selected from hydrogen, —N(R^{7e})—, —OH, —O—C₁-C₄ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl.

In certain embodiments of Formula I, R¹ is selected from —O—, —NH— and —N(C₁-C₃ alkyl-OH)—. In one aspect of these embodiments, R¹ is selected from —O—, —NH— and —N(CH₂CH₂OH)—.

In other embodiments of Formula I, R¹ is selected from —O—, —NH— and —N(CH₃)—.

In still other embodiments of Formula I, when the —C(O)— group adjacent to R¹ is bound directly to an —N(R^{7h})— in R³, R¹ is —CH₂—.

In certain embodiments of Formula I, R² is an optionally substituted C₅-C₁₂ alkylene, optionally substituted C₅-C₁₂ alkenylene, or optionally substituted C₅-C₁₂ alkynylene, wherein:

up to three methylene units of R² are optionally and independently replaced with —O—, —N(R^c)—, —S—, —S(O)—, or —S(O)₂—, wherein R^c is selected from hydrogen, C₁-C₄ alkyl, C(O)—C₁-C₃ alkyl, C(O)—(C₁-C₃ alkylene)-aryl, C(O)—(C₁-C₃ alkylene)-heteroaryl, S(O)₂—C₁-C₃ alkyl, S(O)₂—(C₁-C₃ alkylene)-aryl, and S(O)₂—(C₁-C₃ alkylene)-heteroaryl;

any two substituents bound to a common carbon atom in R² are optionally taken together to form =O, carbocyclyl or heterocyclyl;

any two substituents bound to different carbon atoms in R² are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl;

any substituent bound to a carbon atom in R² and any one R^c are optionally taken together with any intervening atoms to form heteroaryl or heterocyclyl; and

any substituent bound to two R^c are optionally taken together with any intervening atoms to form a heterocyclyl.

In certain embodiments of Formula I, R² is selected from *—CH(R¹⁰)—(CH₂)₂₋₄—NH—C(O)—(C(R¹¹))₁₋₅—, *—CH(R¹⁰)—(CH₂)₄₋₈—, *—CH(R¹⁰)—(CH₂)₂₋₄—(1,4-phenylene)—NH—C(O)—(C(R¹¹))₁₋₃—, and *—CH(R¹⁰)—(CH₂)₂₋₄—(1,4-phenylene)—; R¹⁰ is selected from hydrogen, —C(O)—O—C₁-C₄ alkyl, and —C(O)—OH; and each R¹¹ is independently selected from hydrogen, benzyl, C₁-C₄ alkyl and C₁-C₄ hydroxyalkyl, wherein no more than two R¹¹ are other than hydrogen; one methylene unit in a

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specified —(CH₂)₂₋₄ or —(CH₂)₄₋₈ portion of R² is optionally replaced with —N(H)— or —N(CH₃)—; and “*” represents a terminus of R² bound to R¹. In one aspect of these embodiments, R² is selected from *—CH(R¹⁰)—(CH₂)₂₋₄—NH—C(O)—(CH₂)₁₋₅—, *—CH(R¹⁰)—(CH₂)₄₋₈—, *—CH(R¹⁰)—(CH₂)₂₋₄—NH—C(O)—C((CH₃)₂)—, *—CH(R¹⁰)—(CH₂)₂₋₄—NH—C(O)—CH(CH₂OH)—, *—CH(R¹⁰)—CH₂—(1,4-phenylene)—NH—C(O)—(CH₂)₁₋₃—, *—CH(R¹⁰)—CH₂—(1,4-phenylene)—, —(CH₂)₈—, *—(CH₂)₂—N(CH₃)—(CH₂)₂—NH—C(O)—CH₂—, and *—(CH₂)₅—NH—C(O)—CH(benzyl)—; and R¹⁰ is selected from hydrogen, —C(O)—O—CH₃, and C(O)—OH.

The term “specified —(CH₂)₂₋₄ or —(CH₂)₄₋₈— portion of R²” as used in the preceding paragraph refers to those embodiments of R² comprising portions that are indicated as —(CH₂)₂₋₄— or —(CH₂)₄₋₈—. For example, when R² is —CH(R¹⁰)—(CH₂)₂₋₄—NH—C(O)—(CH₂)₁₋₅—, only the bolded portion is a “specified —(CH₂)₂₋₄— portion of R².”

In other embodiments of Formula I, R² is selected from *—CH(R¹⁰)—Z—, or *—CH(R¹⁰)—X—CH(R¹⁰)—N(R¹²)—C(O)—CH(R¹¹)—(CH₂)₀₋₂—, wherein:

X is selected from —CH₂—O—CH₂—, —CH₂—N(R¹³)—CH₂—, —CH₂—N(H)—C(O)—, —CH₂—, —(CH₂)₂—, and —(CH₂)₃—;

Z is selected from C₂-C₈ alkylene, C₂-C₈ alkenylene, or C₂-C₈ alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —NH— or —N(CH₃)—;

each R¹⁰ is independently selected from hydrogen, —C(O)OH, and —C(O)OCH₃, wherein at least one R¹⁰ is hydrogen;

R¹¹ is selected from hydrogen, (S)—CH₂OH, (S)—CH₃, (S)—C(CH₃)₃, (S)-benzyl, (R)-benzyl, (S)—CH₂-pyridinyl, (S)-cyclohexyl, (S)—CH₂-cyclohexyl, (S)—(CH₂)₂—COOH, (S)—(CH₂)₂—C(O)NH₂, and (S)—(CH₂)₄—NH₂;

R¹² is selected from hydrogen and —CH₃;

R¹³ is selected from hydrogen and —CH₃; or

R¹³ is optionally taken together with R¹² or the —N((C₀-C₃ alkylene)-Q) portion of R¹ to form a heterocyclyl.

In certain embodiments of Formula I, Z is selected from *—(CH₂)₃₋₉—, *—CH(COOH)—(CH₂)₂₋₈—, *—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—O—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—NH—(CH₂)₂—, *—(CH₂)₂—N(CH₃)—(CH₂)₂—, *—CH₂—C≡C—(CH₂)₄₋₅, and *—CH₂—CH=CH—(CH₂)₄₋₅.

In other embodiments of Formula I, R² is selected from *—(CH₂)₃₋₉—, *—CH(COOH)—(CH₂)₂₋₈—, *—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—O—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—NH—(CH₂)₂—, *—(CH₂)₂—N(CH₃)—(CH₂)₂—, *—CH₂—C≡C—(CH₂)₄₋₅, and *—CH₂—CH=CH—(CH₂)₄₋₅.

In other embodiments of Formula I, R² is selected from *—CH(R¹⁰)—Z— and *—C(H)(R¹⁰)—X—C(H)(R¹⁰)—N(R¹²)—C(O)—C(H)(R¹¹)—(CH₂)₀₋₂—, wherein:

X is selected from —CH₂—O—CH₂—, —CH₂—N(H)—CH₂—, —CH₂—N(CH₃)—CH₂—, —CH₂—, —(CH₂)₂—, and —(CH₂)₃—;

Z is selected from C₂-C₈ alkylene, C₂-C₈ alkenylene, or C₂-C₈ alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —N(H)— or —N(CH₃)—;

each R¹⁰ is independently selected from hydrogen and —(R)—COOH, wherein at least one R¹⁰ is hydrogen;

R¹¹ is selected from hydrogen, (S)—CH₂OH, (S)—CH₃, (S)—C(CH₃)₃, (S)-benzyl, (R)-benzyl, (S)—CH₂-pyridinyl, (S)-cyclohexyl, (S)—CH₂-cyclohexyl, (S)—(CH₂)₂—COOH, (S)—(CH₂)₂—C(O)NH₂, and (S)—(CH₂)₄—NH₂;

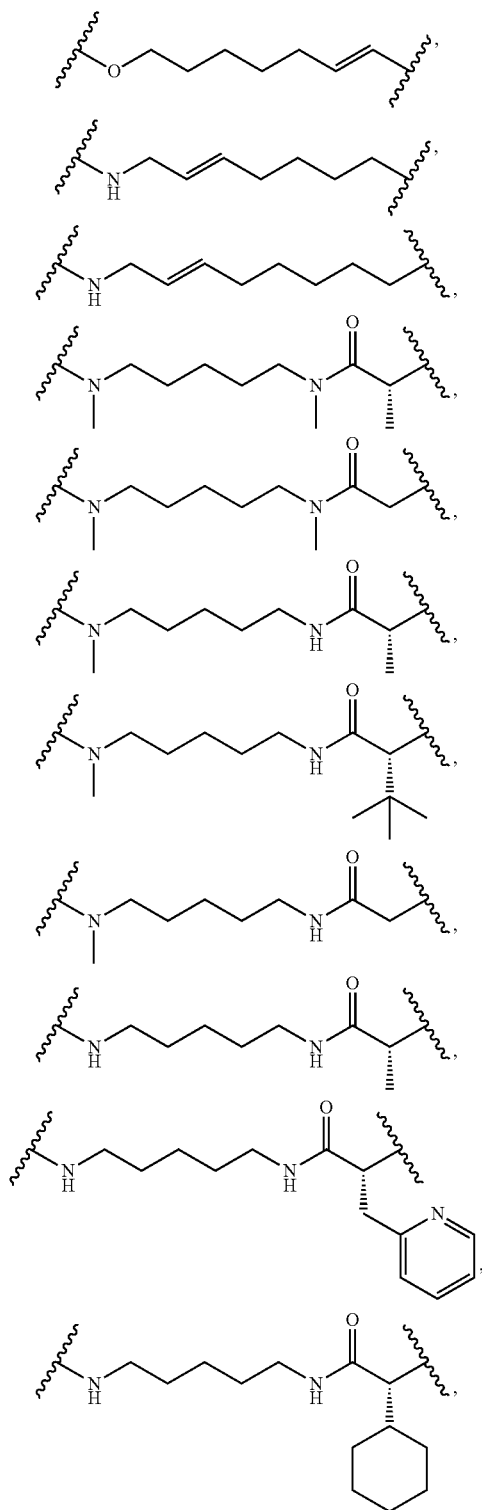
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R^{12} is selected from hydrogen and $-\text{CH}_3$; and

“*” represents a terminus of R^2 bound to R^1 .

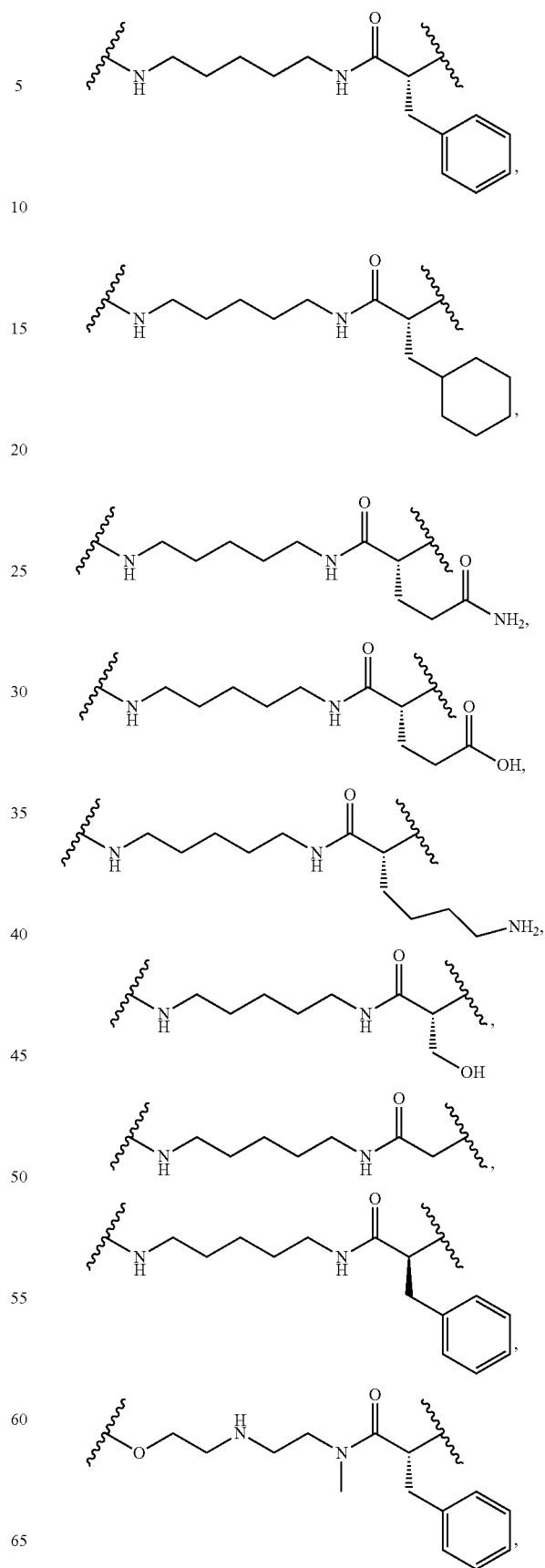
In certain embodiments, $p+q$ is 2, 3, or 4. In other embodiments, $p+q$ is 3.

In a more specific embodiment, the portion of the compound represented by $-R^1-R^2$ is selected from:



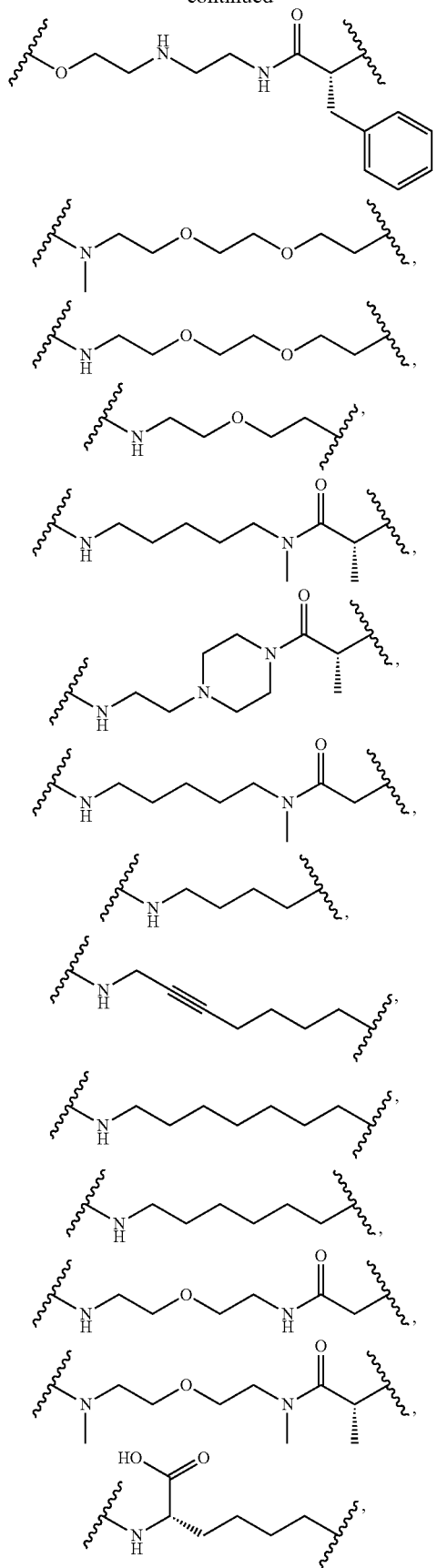
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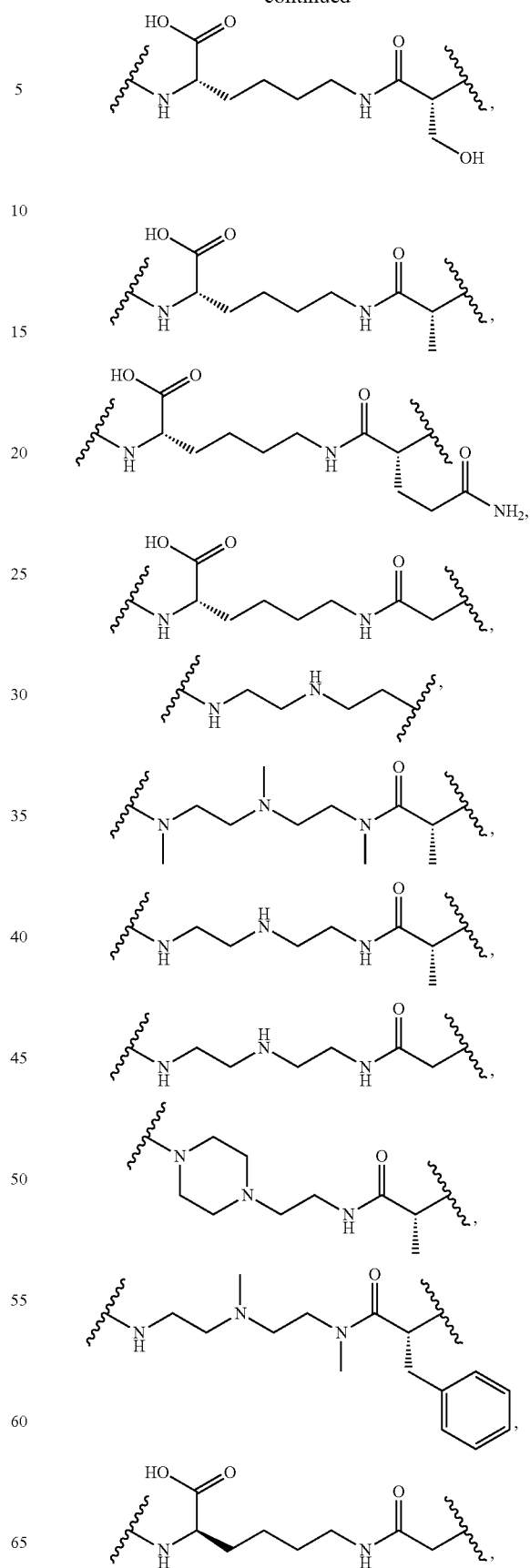
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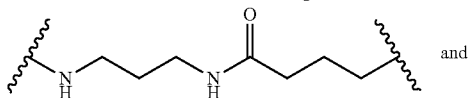
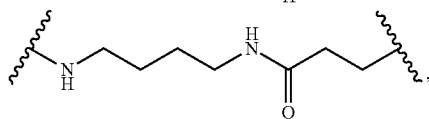
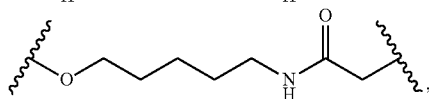
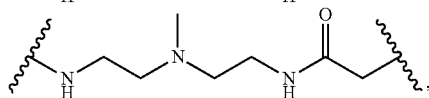
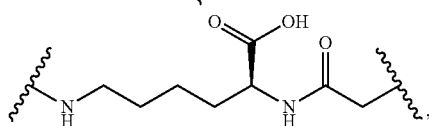
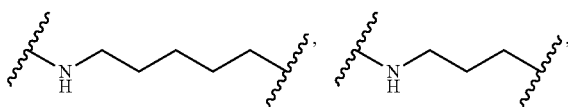
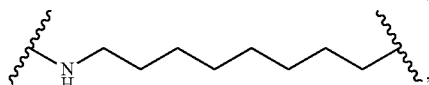
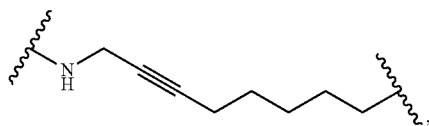
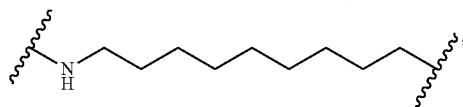
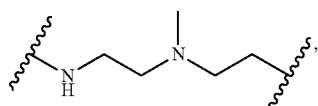
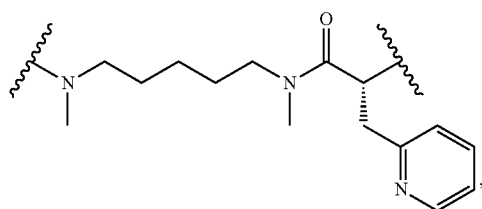
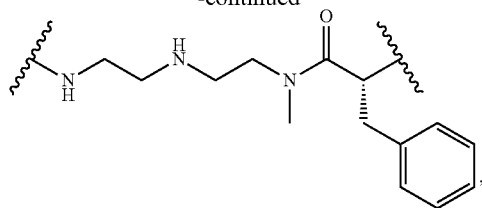
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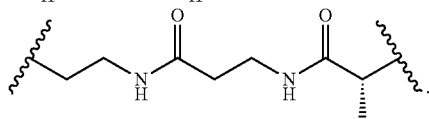


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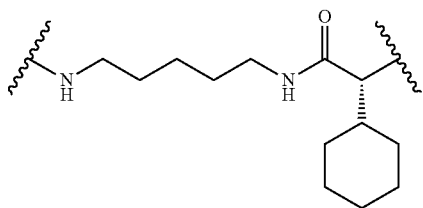
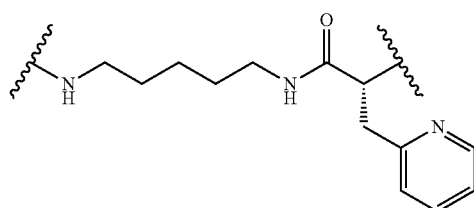
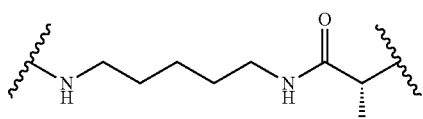
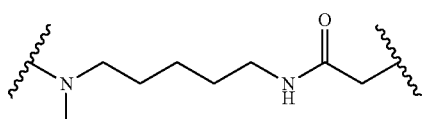
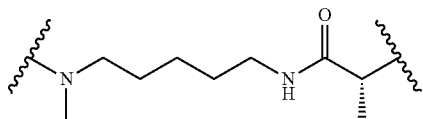
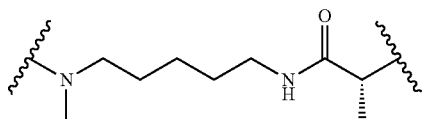
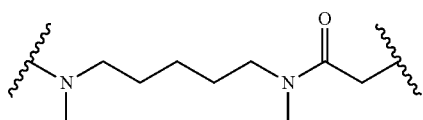
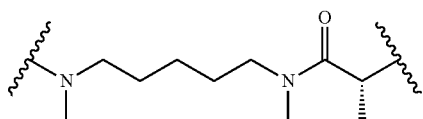
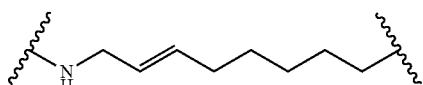
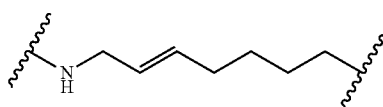
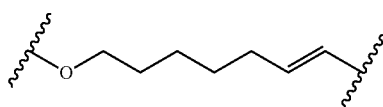


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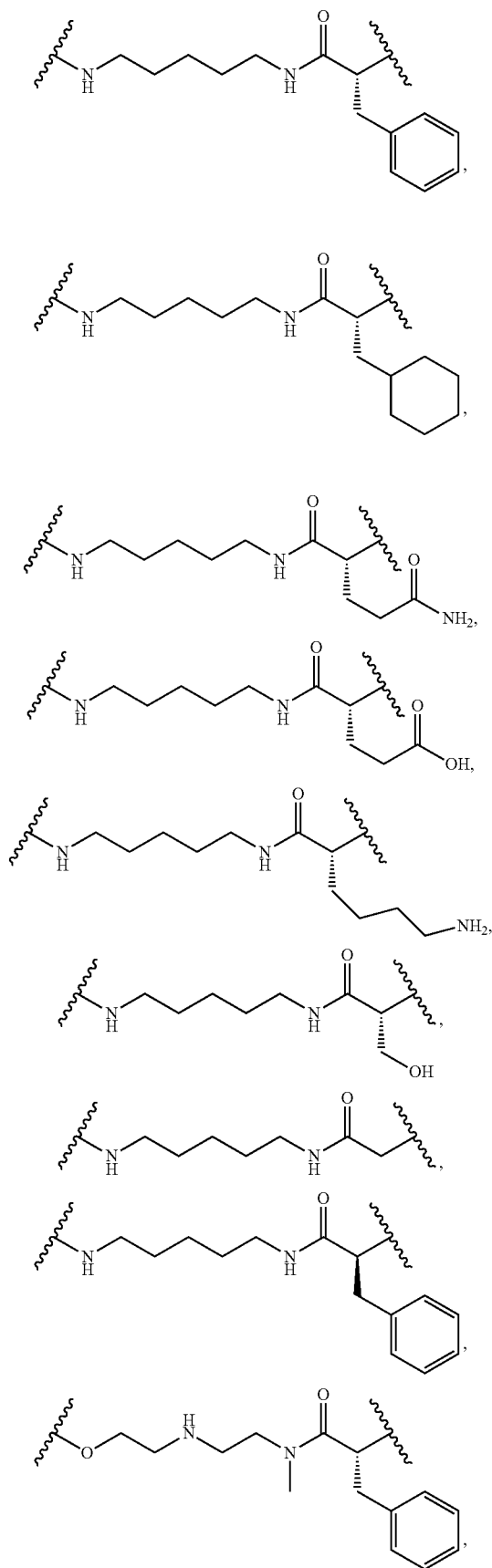
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In certain other embodiments, the portion of the compound represented by $-R^1-R^2$ is selected from:

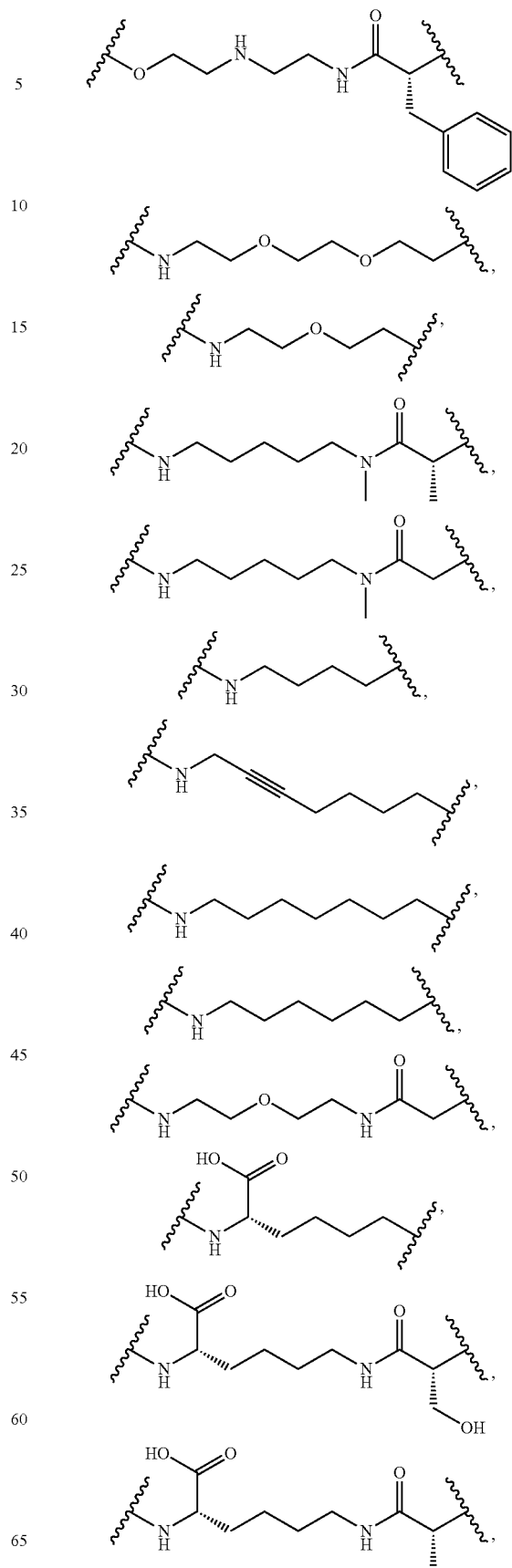


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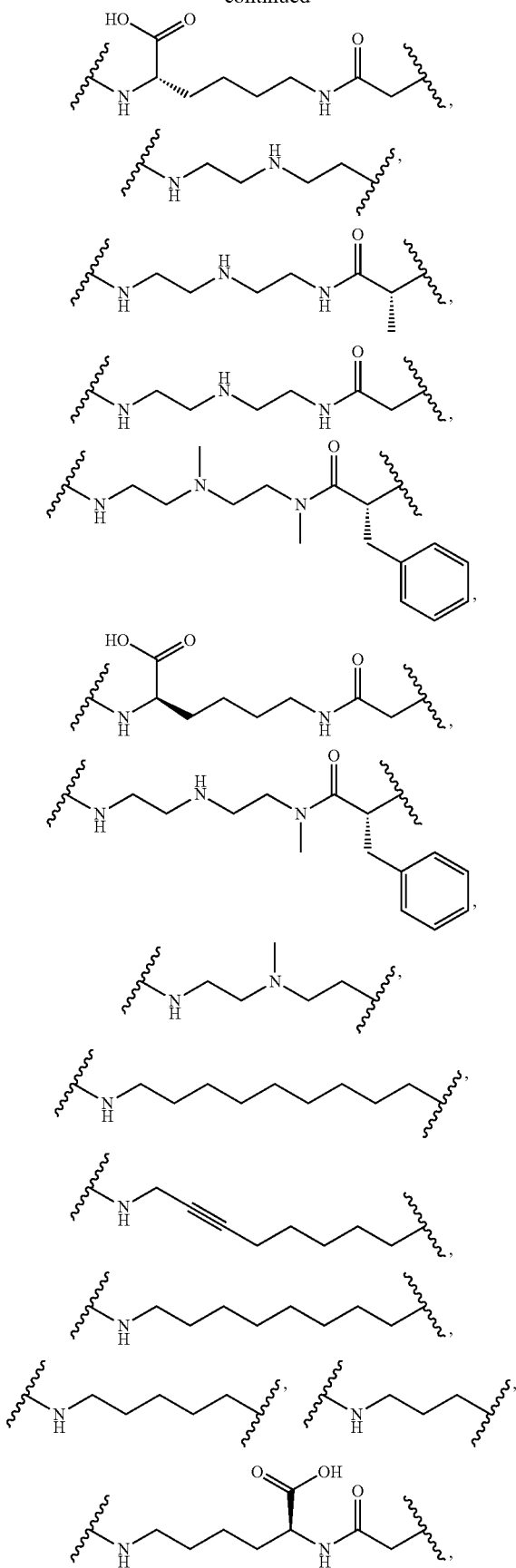
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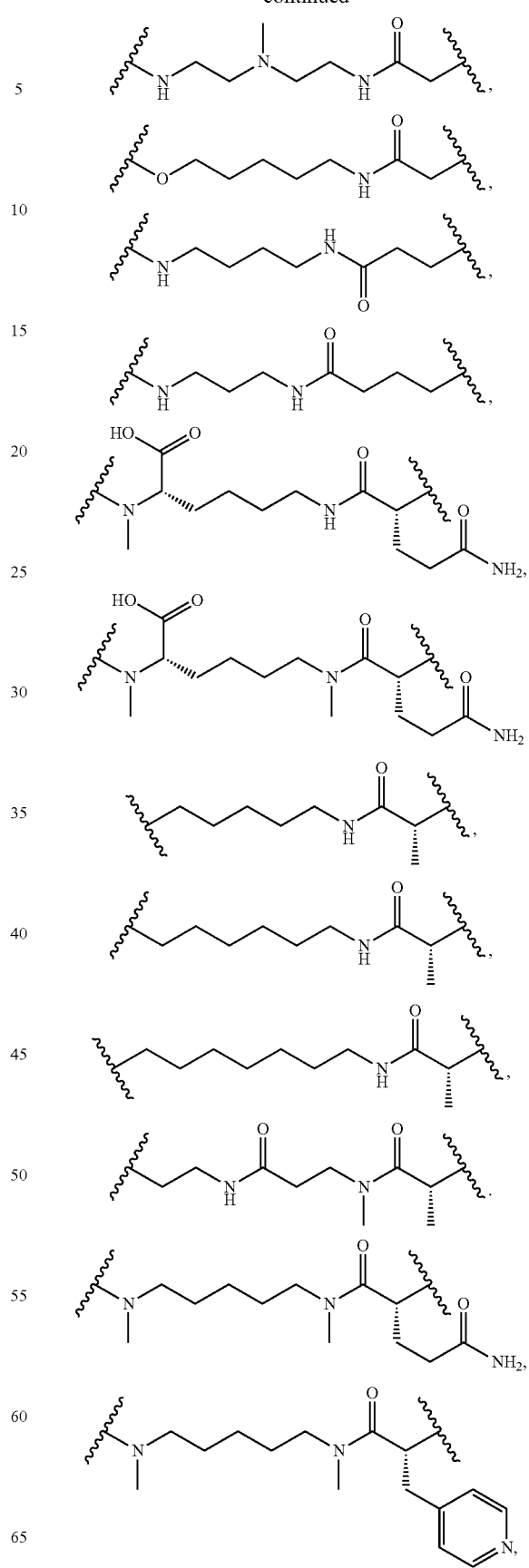


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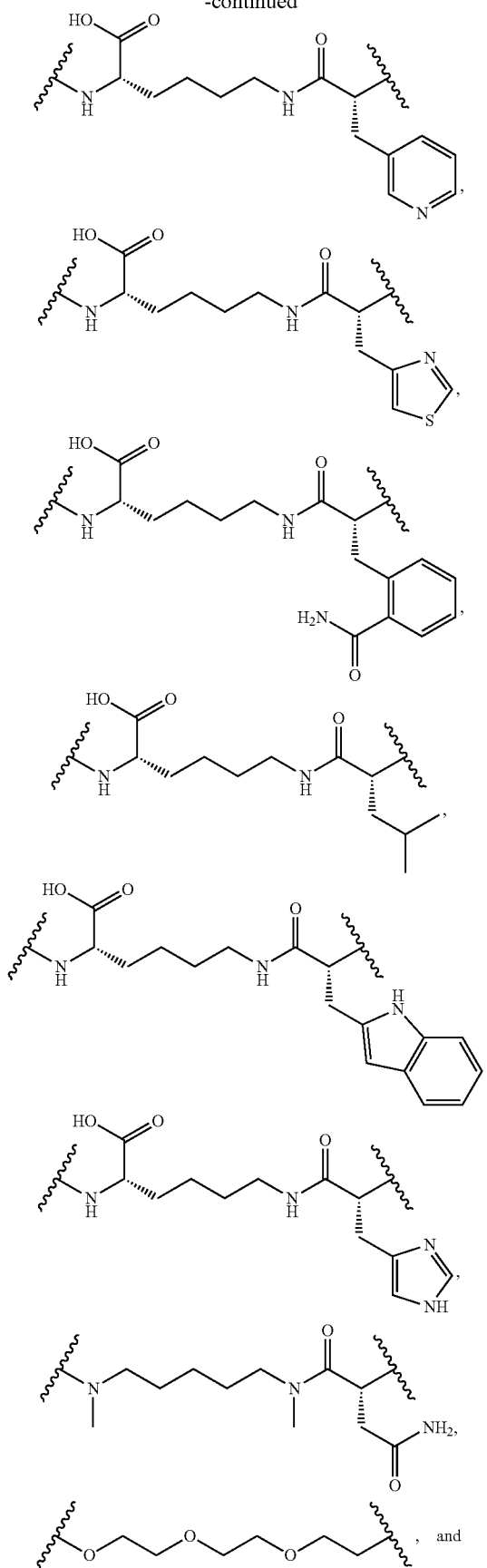
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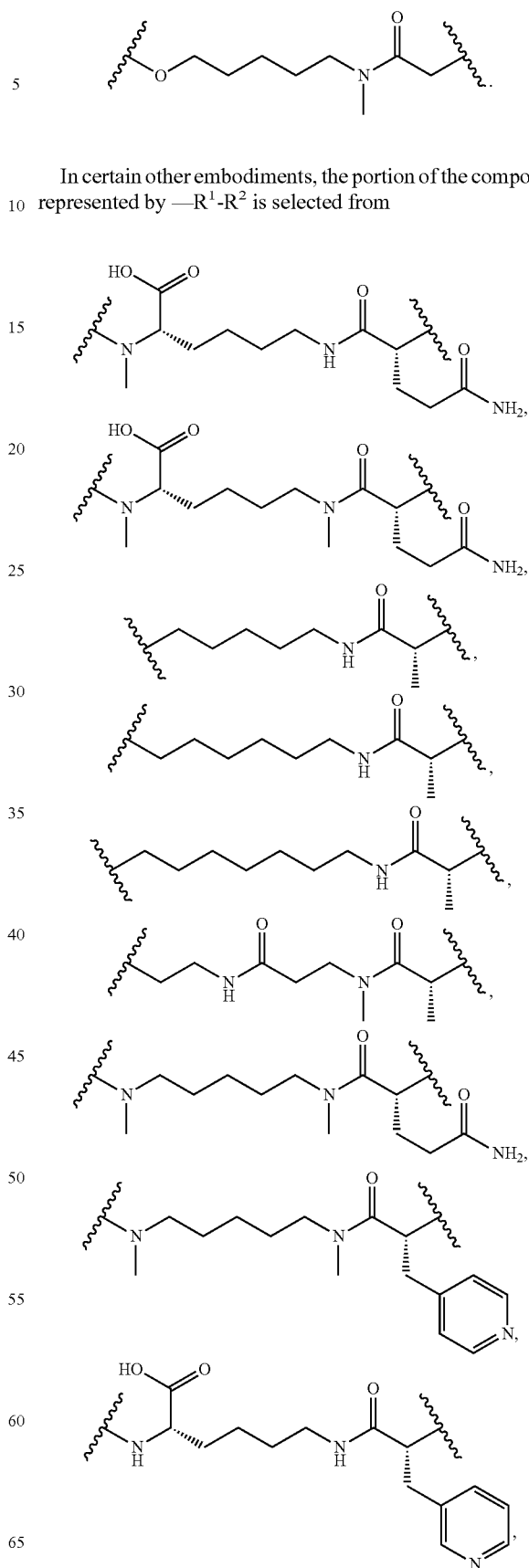


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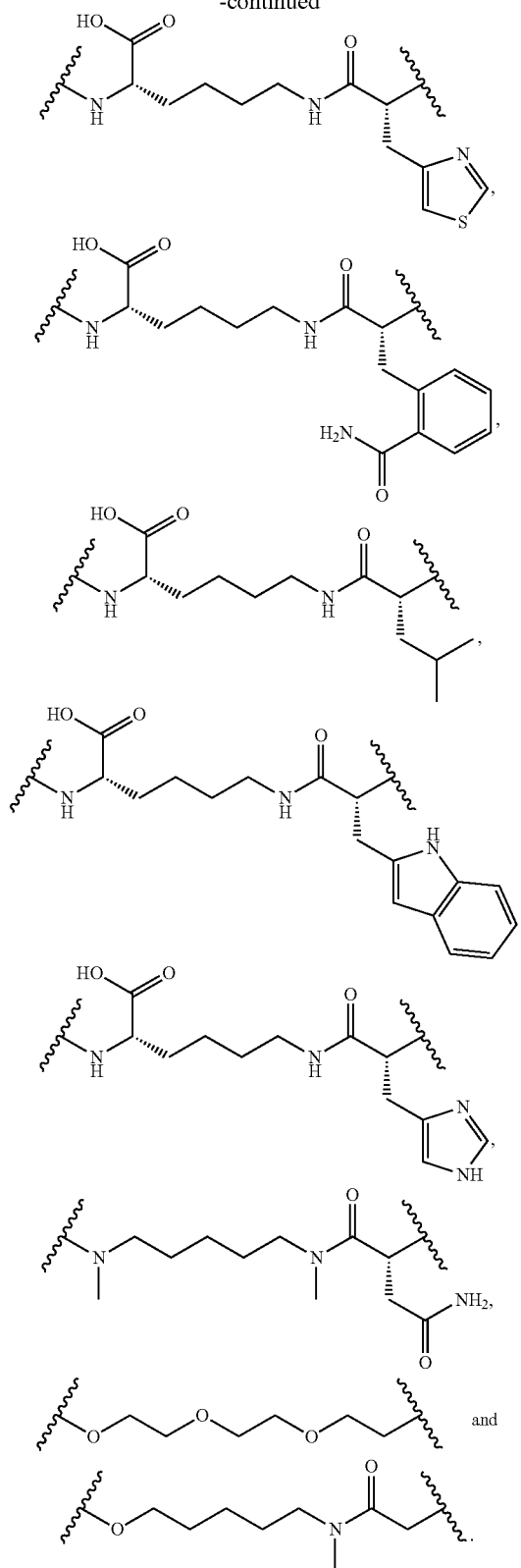
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In certain other embodiments, the portion of the compound represented by $-R^1-R^2$ is selected from

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In certain embodiments of Formula I, R³ is $-\text{[C(R}^d\text{)(R}^d\text{)]}_{2-4}-$, wherein:

each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally

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taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl.

In certain embodiments of Formula I, R³ is $\text{†-N(R}^{7h}\text{)-[C(R}^d\text{)(R}^d\text{)]}_2-$, wherein:

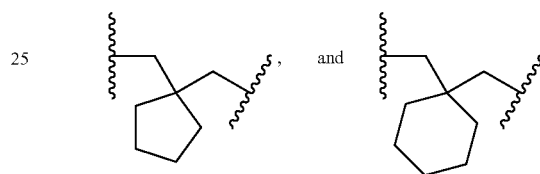
each R^d is independently selected from hydrogen and a suitable alkylene substituent;

any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl; and

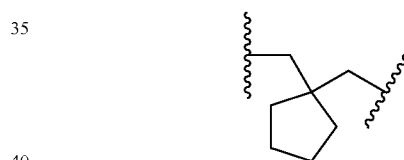
“†” represents a portion of R³ bound to R¹.

In certain embodiments of Formula I, R³ is $-\text{[C(R}^d\text{)(R}^d\text{)]-N(R}^{7h}\text{)-[C(R}^d\text{)(R}^d\text{)]}-$, wherein: each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl.

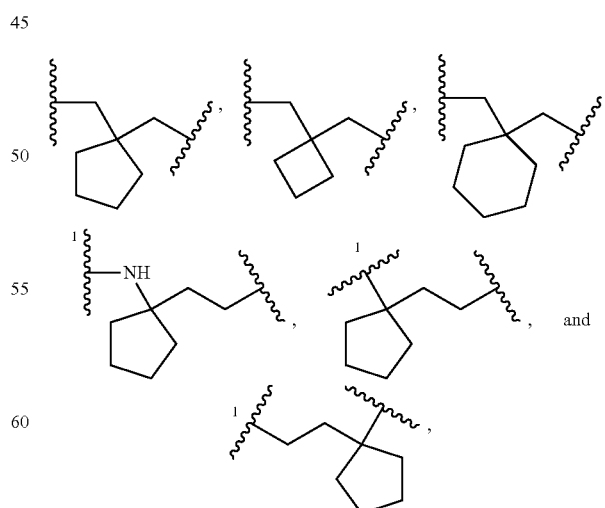
In certain embodiments of Formula I, R³ is selected from $-(\text{CH}_2)_3-$, $-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{CH}_2-$,



In one aspect of these embodiments, R³ is



In certain embodiments of Formula I, R³ is selected from $-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2-$,

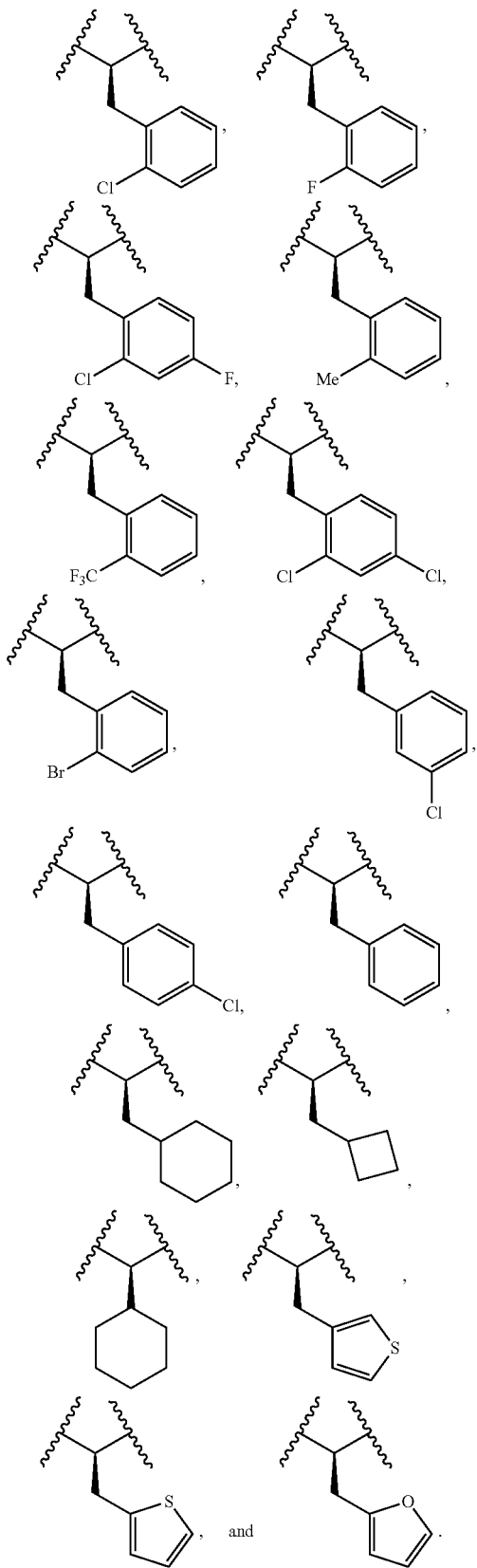


wherein “1” represents a portion of R³ bound to the carbonyl moiety that is bound to R¹.

In certain other embodiments, R^5 is $-\text{C}(\text{H})((\text{R})\text{-benzyl})$ - wherein a phenyl portion of the benzyl is optionally substituted with up to two substituents independently selected from bromo, chloro, fluoro, methyl, and $-\text{CF}_3$; or R^5 is selected from $-\text{C}(\text{H})(\text{CH}_2-\text{C}_4\text{-C}_6 \text{ cycloalkyl})$ -, $-\text{C}(\text{H})(\text{C}_4\text{-C}_6 \text{ cycloalkyl})$ -, $-\text{C}(\text{H})(\text{CH}_2\text{-thienyl})$ -, $-\text{C}(\text{H})(\text{CH}_2\text{-furanlyl})$ -, $-\text{C}(\text{H})(\text{heterocyclyl})$ -, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)\text{-(aryl)})$ -, $-\text{C}(\text{H})$ 60 $\text{CH}(\text{CH}_3)\text{-(heteroaryl)}$ -, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)\text{-(heterocyclyl)})$ -, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)\text{-(carbocyclyl)})$ -, and $-\text{C}(\text{H})(\text{C}_3\text{-C}_4 \text{ alkyl})$ -.

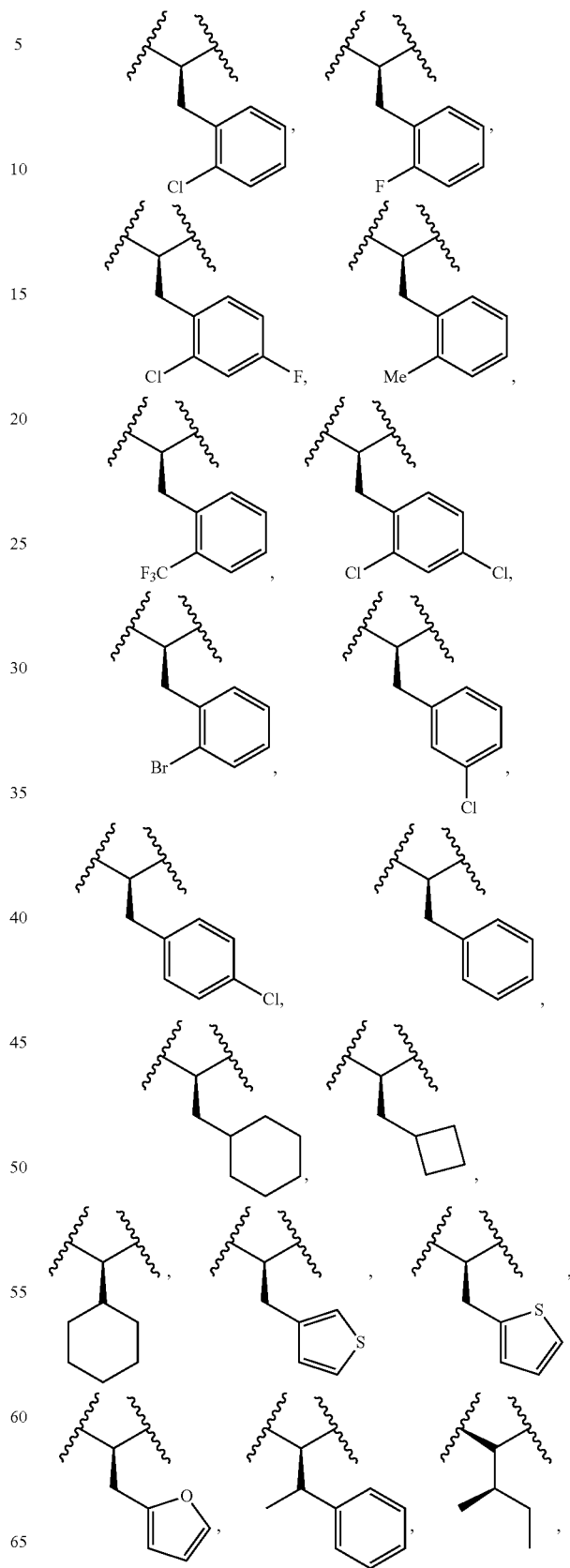
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In a more specific embodiment, R^5 is selected from:

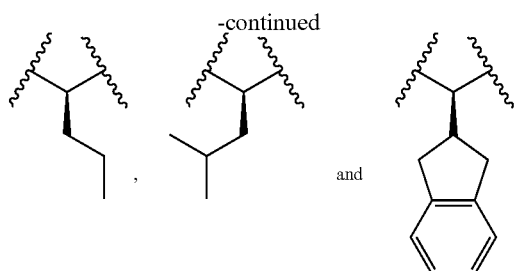


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In another more specific embodiment, R^5 is selected from:

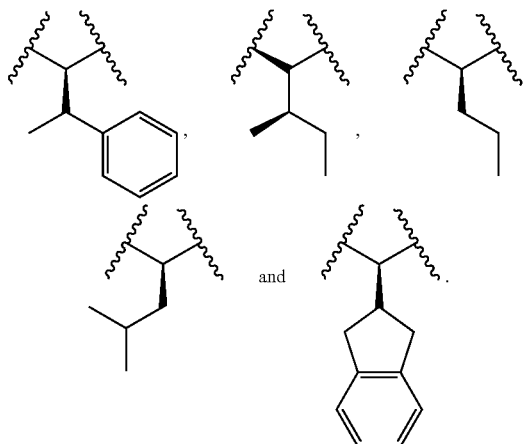


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In certain other embodiments, R^5 is selected from $-\text{C}(\text{H})$ (heterocyclyl)-, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)(\text{aryl})-$, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)(\text{heteroaryl})-$, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)(\text{heterocyclyl})-$, $-\text{C}(\text{H})(\text{CH}(\text{CH}_3)(\text{carbocyclyl})-$, and $-\text{C}(\text{H})(\text{C}_3\text{-C}_4$ alkyl)-. In

In certain other embodiments, R^5 is selected from



In certain embodiments of Formula I, R^6 is selected from heteroaryl, $-\text{C}(\text{O})-\text{R}^8$, $-\text{C}(\text{O})-\text{O}-\text{R}^8$, $-\text{C}(\text{O})-\text{C}(\text{O})-\text{R}^8$, $-\text{S}(\text{O})-\text{R}^8$, $-\text{S}(\text{O})_2-\text{R}^8$, $\text{C}(\text{O})-\text{N}(\text{R}^{7a})-\text{R}^8$, and $-\text{S}(\text{O})_2-\text{N}(\text{R}^{7b})-\text{R}^8$, wherein each R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{7f} , R^{7g} is independently selected from hydrogen and $\text{C}_1\text{-C}_4$ alkyl; and R^8 is as defined above.

In certain embodiments of Formula I, R^6 is $-\text{C}(\text{O})-[\text{CH}_2]_{0-1}-\text{R}^9$; and R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and $\text{C}_1\text{-C}_4$ alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, hydroxy, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ hydroxyalkyl. In one aspect of these embodiments, R^9 is selected from phenyl, pyridinyl, oxazolyl, pyrazinyl, pyrimidinyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, $-\text{OCH}_3$, and $\text{C}_1\text{-C}_4$ alkyl, wherein any phenyl, pyridinyl, oxazolyl, pyrazinyl, or pyrimidinyl in R^9 is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, CF_3 , hydroxy, and $-\text{CH}_2\text{OH}$.

In alternate embodiments of Formula I, R^6 is $-\text{C}(\text{O})-[\text{C}(\text{R}^{13})_2]_{0-1}-\text{R}^{9a}$, wherein R^{9a} is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, $\text{C}_1\text{-C}_4$ alkyl, $-\text{O}-\text{C}_1\text{-C}_4$ alkyl, $-\text{NH}-\text{CH}_3$, $-\text{N}(\text{CH}_3)_2$, and $-\text{NH}-\text{CH}_2\text{-aryl}$, wherein

any aryl, heteroaryl, cycloalkyl, or saturated heterocyclyl portion of R^{9a} is optionally substituted with up to 2 substituents independently selected from halo, $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ haloalkyl, hydroxy, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{O}-(\text{CH}_2)_2\text{-morpholin-4-yl}$, $-\text{N}(\text{C}_1\text{-C}_3\text{ alkyl})_2$, an N-linked saturated heterocycle,

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$-\text{O}-(\text{CH}_2)_2-\text{N}(\text{R}^{14})-\text{CH}_2\text{-phenyl}$, $-\text{NH}-\text{C}(\text{O})-\text{CH}_2-\text{NH}-\text{CH}_2\text{-phenyl}$, and $-\text{O}-(\text{CH}_2)_2-\text{N}(\text{R}^{14})_2$;

each R^{13} is independently selected from hydrogen or fluoro, or

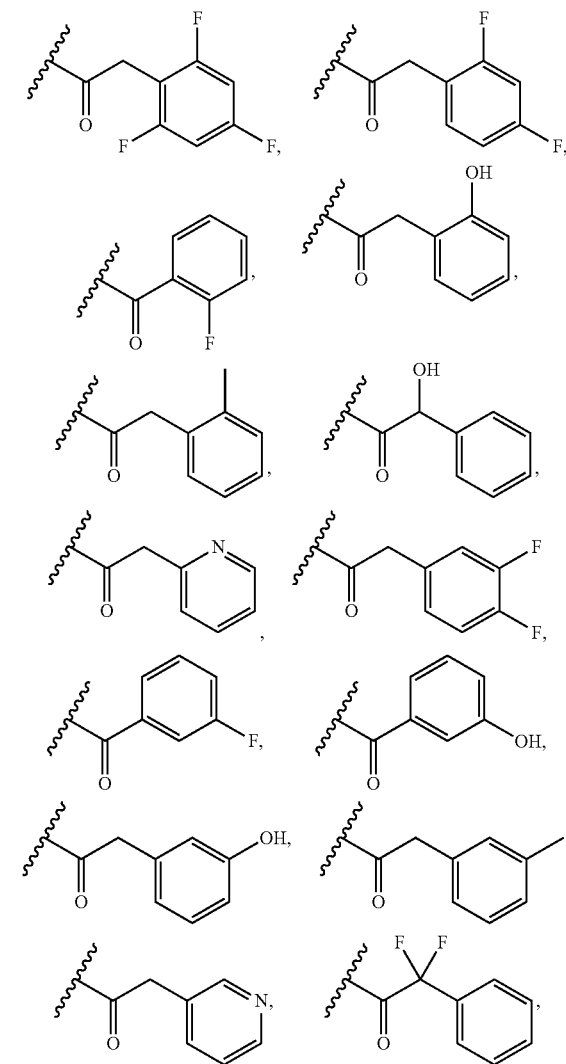
two R^{13} are taken together to form a $\text{C}_3\text{-C}_6$ cycloalkyl or $=\text{O}$; and

each R^{14} is independently hydrogen or $-\text{CH}_3$.

In certain embodiments, R^{9a} is selected from phenyl, pyridyl, quinolinyl, isoquinolinyl, cyclohexyl, 3,3-difluorocyclopropyl, $-\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{OCH}_3$, $-\text{N}(\text{CH}_3)_2$, $-\text{NH}(\text{CH}_3)$, $-\text{NH-benzyl}$, wherein R^{9a} is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, methyl, methoxy, hydroxy, $-\text{O}-(\text{CH}_2)_2\text{-morpholin-4-yl}$, $-\text{O}-(\text{CH}_2)_2-\text{N}(\text{CH}_3)-\text{CH}_2\text{-phenyl}$, and $-\text{O}-(\text{CH}_2)_2-\text{N}(\text{CH}_3)_2$.

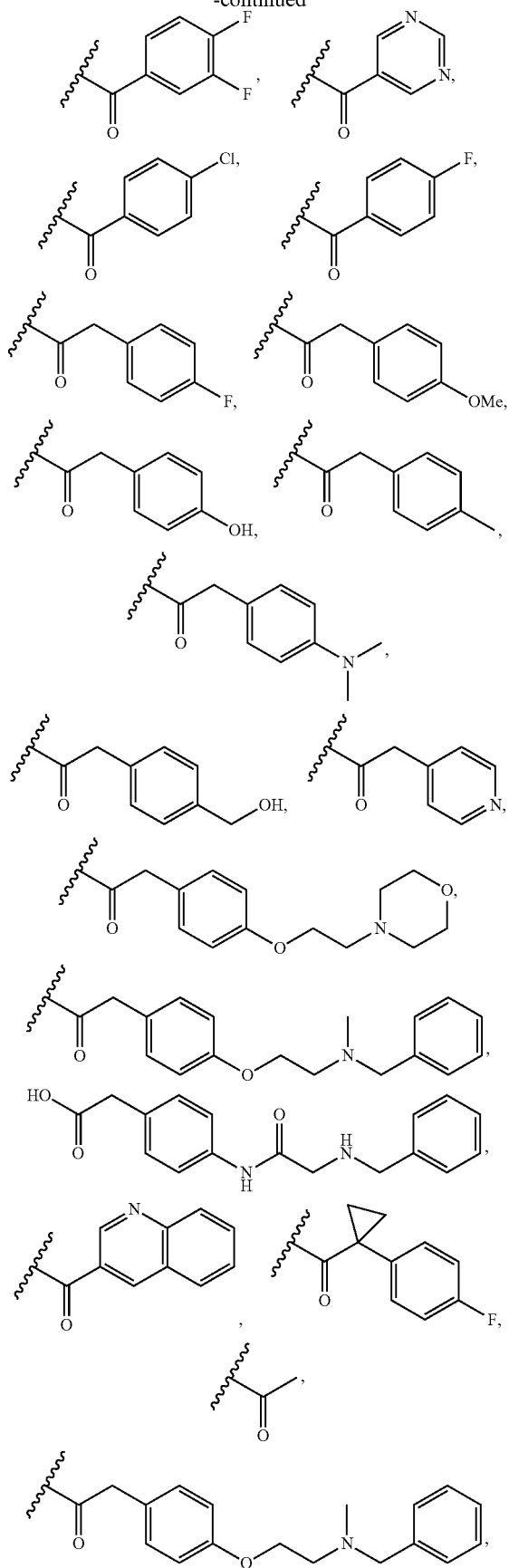
In certain embodiments, R^6 is $-\text{C}(\text{O})\text{-benzyl}$ or $-\text{C}(\text{O})\text{-phenyl}$, wherein the benzyl and phenyl in R^6 are each optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, $\text{C}_1\text{-C}_4$ alkoxy, and $\text{C}_1\text{-C}_4$ alkyl.

In certain embodiments, R^6 is selected from:



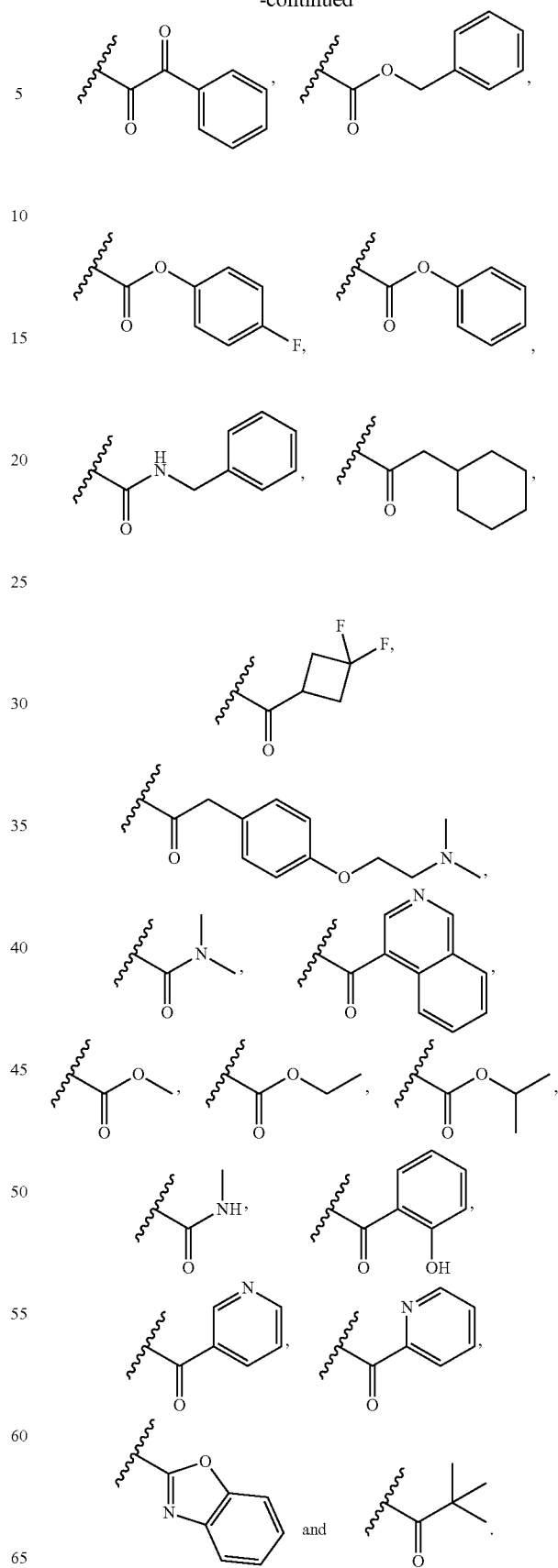
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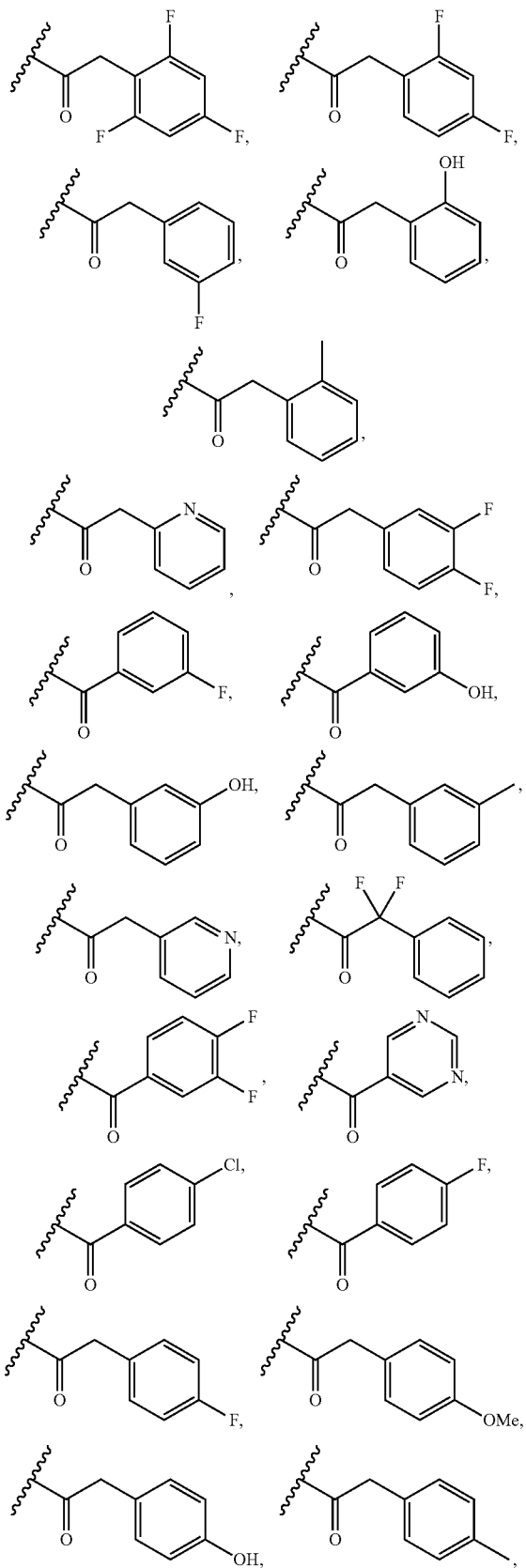
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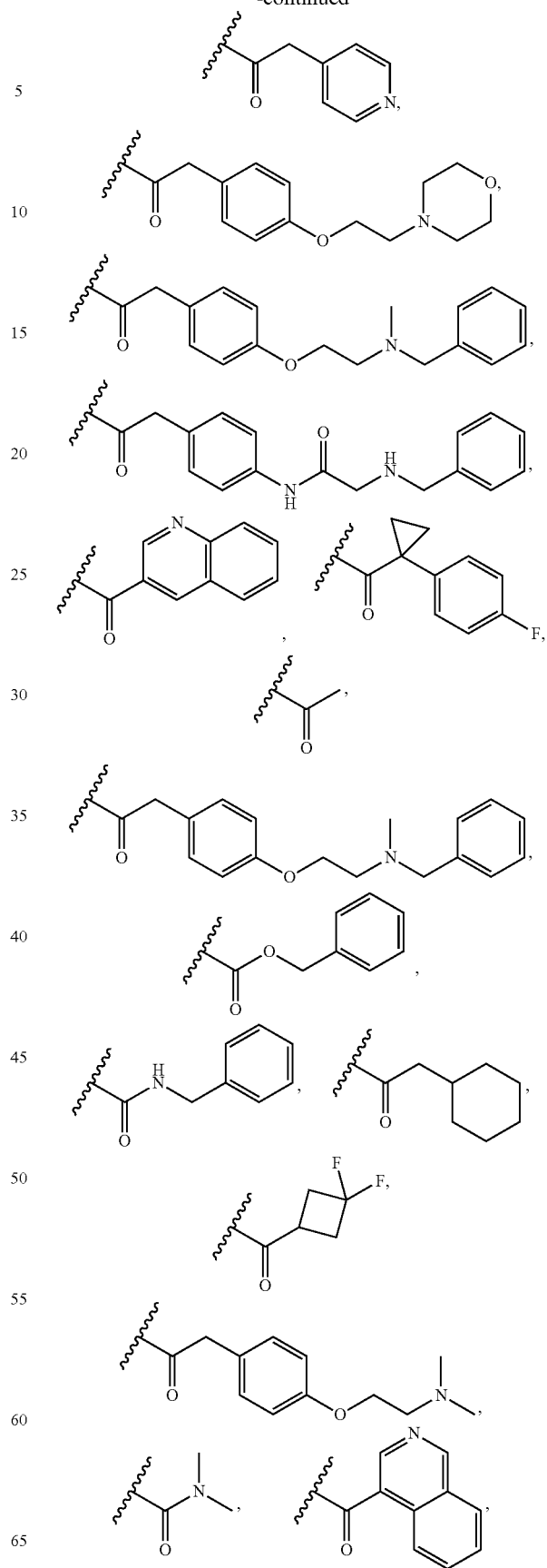
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In certain embodiments, R^6 is selected from:



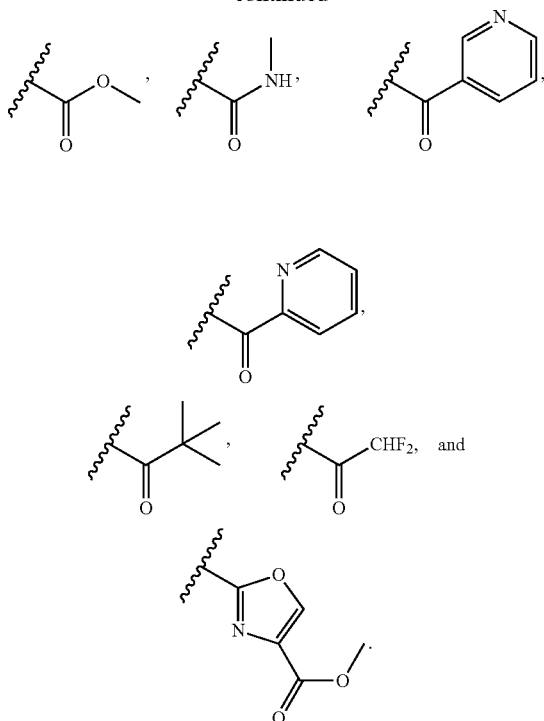
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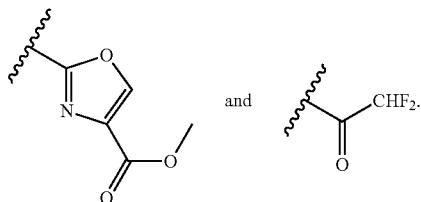


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In certain other embodiments, R^6 is selected from



In certain embodiments of Formula I, R^{7a} , R^{7b} , R^{7c} , R^{7d} , R^{7e} , R^{7f} , R^{7g} are independently selected from methyl and hydrogen.

Certain other embodiments relate to a compound of Formula I wherein rather than R^{7d} and R^6 being optionally taken together to form a heterocyclyl, R^{7d} and R^8 are optionally taken together to form a heterocyclyl.

The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments.

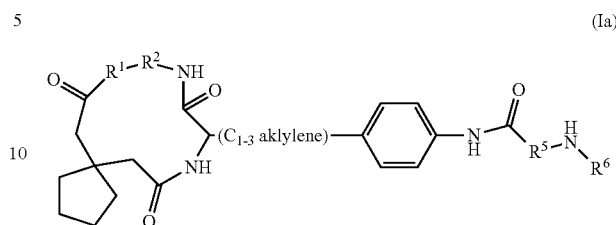
Exemplary specified compounds of Formula I are set forth in FIG. 12.

In one embodiment, the compound of Formula I is selected from any one of the compounds set forth in FIG. 12.

Any of the compounds of Formula I, may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like; N may be in any isotopic form, including ^{14}N and ^{15}N .

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In yet other embodiments, the invention provides a compound represented by Formula Ia:



or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-\text{N}(\text{H})-$;

R^2 is one of the following:

(a) $-\text{alkylene}-\text{N}(\text{H})\text{C}(\text{O})-\text{alkylene}-\psi$,

(b) $-\text{C}(\text{H})(\text{CO}_2\text{H})-\text{alkylene}-\text{N}(\text{H})\text{C}(\text{O})-\text{alkylene}-\psi$, or

(c) $-\text{alkylene}-\text{O}-\text{alkylene}-\text{O}-\text{alkylene}-\psi$; where ψ is a bond to the nitrogen atom in R^1 ;

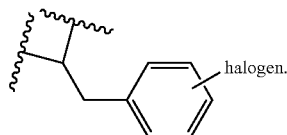
R^5 is C_1-C_2 alkylene substituted with one $-(\text{C}_1-\text{C}_5 \text{ alkylene})-\text{aryl}$ that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl;

R^6 is $-\text{C}(\text{O})-\text{R}^8$ or $-\text{C}(\text{O})-\text{O}-\text{R}^8$;

R^8 is (a) C_1-C_6 alkyl or (b) $-(\text{C}_1-\text{C}_3 \text{ alkylene})-\text{aryl}$ optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl.

In certain embodiments, R^2 is $-\text{alkylene}-\text{N}(\text{H})\text{C}(\text{O})-\text{alkylene}-\psi$.

In certain embodiments, R^5 is



In certain embodiments, R^6 is $-\text{C}(\text{O})-\text{R}^8$.

In certain embodiments, $R^8-(\text{C}_1-\text{C}_3 \text{ alkylene})-\text{aryl}$ optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl. In certain other embodiments, R^8 is benzyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl.

The description above describes multiple embodiments relating to compounds of Formula Ia. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula Ia wherein R^5 is C_1-C_2 alkylene substituted with one $-(\text{C}_1-\text{C}_5 \text{ alkylene})-\text{aryl}$ that is optionally substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_5 alkyl, hydroxyl, and C_1-C_3 haloalkyl; and R^6 is $-\text{C}(\text{O})-\text{O}-\text{R}^8$.

Unless otherwise indicated when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

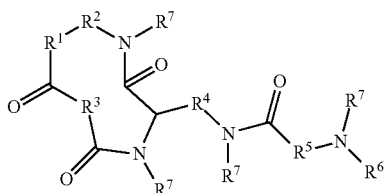
The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention

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expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

A. Additional Exemplary Macrocyclic Compounds

An additional family of compounds of the invention is represented by Formula II:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from —O— and —N((C₀-C₃ alkylene)-Q)-, wherein Q is selected from hydrogen, —N(R⁷), —OH, —O—C₁-C₄ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R² is C₅-C₁₂ alkylene, alkenylene or alkynylene, each of which is optionally substituted and wherein:

up to three methylene units of R² are optionally and independently replaced with —O—, —N(R^c), —S—, —S(O)—, or —S(O)₂—, wherein R^c is selected from hydrogen, C₁-C₄ alkyl, —C(O)—C₁-C₃ alkyl, —C(O)—(C₁-C₃ alkylene)-aryl, —C(O)—(C₁-C₃ alkylene)-heteroaryl, —S(O)₂-C₁-C₃ alkyl, —S(O)₂-(C₁-C₃ alkylene)-aryl, and —S(O)₂-(C₁-C₃ alkylene)-heteroaryl;

any two substituents bound to a common carbon atom in R² are optionally taken together to form =O, carbocyclyl or heterocyclyl;

any two substituents bound to different carbon atoms in R² are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl; and

any substituent bound to a carbon atom in R² and any one R^c are optionally taken together with any intervening atoms to form heteroaryl or heterocyclyl;

R³ is optionally substituted —(C₂-C₄ alkylene)-, wherein any two substituents on R³ are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl or heterocyclyl;

R⁴ is —(C_n alkylene)-Y—(C_m alkylene)-, wherein:

each alkylene portion of R⁴ is optionally and independently substituted;

Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl and optionally substituted C₁-C₃ alkylene;

each of n and m are independently selected from 0, 1, 2, 3, 4, 5 and 6; and

n+m is 6 or less;

R⁵ is C₁-C₂ alkylene substituted with one or more —(C₀-C₅ alkylene)-R^f, wherein each R^f is independently selected from —CH₃, —O—C₁-C₃ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R⁶ is selected from heteroaryl, —C(O)—R⁸, —S(O)—R⁸, —S(O)₂-R⁸, —C(O)—N(R⁷)-R⁸, and —S(O)₂-N(R⁷)-R⁸;

each R⁷ is independently selected from hydrogen and C₁-C₄ alkyl;

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R⁸ is selected from —(C₀-C₆ alkylene)-aryl, —(C₀-C₆ alkylene)-heteroaryl, —(C₀-C₆ alkylene)-carbocyclyl, —(C₀-C₆ alkylene)-heterocyclyl, and C₁-C₆ alkyl, wherein when R⁸ is C₁-C₆ alkyl, up to two methylene units in the alkyl are optionally and independently replaced with —O—, —N(R⁷), —S—, —S(O)—, or —S(O)₂—; and

any alkyl or alkylene portion of R⁸ is optionally substituted with an appropriate alkyl or alkylene substituent other than =O; or

R⁷ and R⁸ are optionally taken together to form a heterocyclyl; and

any aryl, heteroaryl, carbocyclyl or heterocyclyl portion of the compound is optionally substituted.

It will be understood by those of skill in the art that because the compounds of the invention are limited to compounds that are stable, compounds formed by the optional and independent replacement of up to three methylene units in R² with certain combinations of —O—, —S—, —S(O)—, —S(O)₂—, or —NR^c— are not within the scope of the present invention. For example, compounds wherein the R² moiety comprises an —O—, —S—, —S(O)—, —S(O)₂—, or —N(R^c)—, adjacent to an —O—, —S—, —S(O)—, —S(O)₂—, or —N(R^c)— are not within the scope of the present invention, except for an —S(O)₂— adjacent a —N(R^c)—. In addition, R² should not comprise —O—CH₂—O—, —N—CH₂—O—, or —O—CH₂—N—, wherein the —CH₂— portion thereof is optionally substituted, except when the —CH₂— portion is substituted to become —C(O)—.

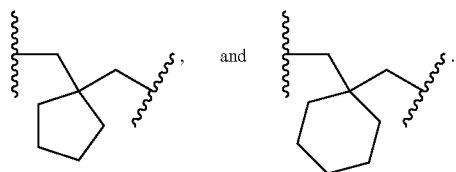
In certain embodiments of Formula II, R¹ is selected from —O—, —NH— and —N(C₁-C₄ alkyl-OH)—. In one aspect of these embodiments, R¹ is selected from —O—, —NH— and —N(CH₂CH₂OH)—.

In certain embodiments of Formula II, R² is selected from *—C(H)(R¹⁰)-(CH₂)₂₋₄-N(H)-C(O)-(C(R¹¹))₂₋₅—, *—C(H)(R¹⁰)-(CH₂)₄₋₈—, *—C(H)(R¹⁰)-(CH₂)₂₋₄-(1,4-phenylene)-N(H)-C(O)-(C(R¹¹))₂₋₃—, and *—C(H)(R¹⁰)-(CH₂)₂₋₄-(1,4-phenylene)-; R¹⁰ is selected from hydrogen, —C(O)—O—C₁-C₄ alkyl, and —C(O)—OH; and each R¹¹ is independently selected from hydrogen, benzyl, C₁-C₄ alkyl and C₁-C₄ hydroxyalkyl, wherein no more than two R¹¹ are other than hydrogen; one methylene unit in a specified —(CH₂)₂₋₄ or —(CH₂)₄₋₈ portion of R² is optionally replaced with —N(R⁷); and “*” represents a terminus of R² bound to R¹. In one aspect of these embodiments, R² is selected from *—C(H)(R¹⁰)-(CH₂)₂₋₄-N(H)-C(O)-(CH₂)₁₋₅—, *—C(H)(R¹⁰)-(CH₂)₄—, *—C(H)(R¹⁰)-(CH₂)₂₋₄-N(H)-C(O)-C((CH₃)₂)—, *—C(H)(R¹⁰)-(CH₂)₂₋₄-N(H)-C(O)-C(H)(CH₂OH)—, *—C(H)(R¹⁰)-CH₂-(1,4-phenylene)-N(H)-C(O)-(CH₂)₁₋₃—, *—C(H)(R¹⁰)-CH₂-(1,4-phenylene)-, —(CH₂)₈—, *—(CH₂)₂-N(CH₃)-(CH₂)₂-N(H)-C(O)-CH₂—, and *—(CH₂)₅-N(H)-C(O)-C(H)(benzyl)-; and R¹⁰ is selected from hydrogen, —C(O)—O—CH₃, and C(O)—OH.

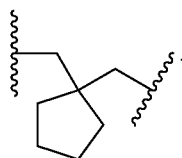
The term “specified —(CH₂)₂₋₄— or —(CH₂)₄₋₈— portion of R²” as used in the preceding paragraph refers to the portion of those choices for R² that are indicated as —(CH₂)₂₋₄— or —(CH₂)₄₋₈—. For example, when R² is —C(H)(R¹⁰)-(CH₂)₂₋₄-N(H)-C(O)-(CH₂)₁₋₅—, only the bolded portion is a “specified —(CH₂)₂₋₄— portion of R².”

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In certain embodiments of Formula II, R^3 is selected from $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$,



In one aspect of these embodiments, R^3 is



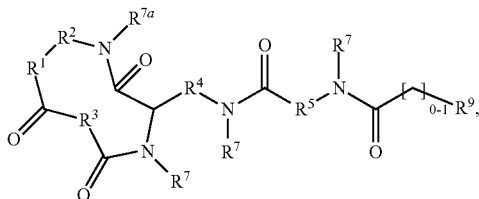
In certain embodiments of Formula II, R^4 is selected from $-(CH_2)_4-$, and $-CH_2-(1,4\text{-phenylene})-$, wherein “*” represents a portion of R^4 bound to $N(R^7)$.

In certain embodiments of Formula II, R^5 is selected from $-CH-(C_1-C_4 \text{ alkyl})$, $-CH-CH_2\text{-aryl}$, $-CH-CH_2\text{-heteroaryl}$, $-CH-CH_2\text{-cycloalkyl}$, and $-CH\text{-cycloalkyl}$, wherein the aryl or heteroaryl is optionally substituted with up to two substituents independently selected from halo, C_1-C_4 alkyl, and phenyl. In one aspect of these embodiments, R^5 is selected from $-CH-C(CH_3)_3$, $-CH-CH(CH_2CH_3)-CH_3$, $-CH\text{-cyclohexyl}$, $-CH-CH_2\text{-furanlyl}$, $-CH-CH_2\text{-phenyl}$, $-CH-CH_2\text{-biphenyl}$, $-CH-CH_2\text{-thiophenyl}$, $-CH-CH_2\text{-thiazolyl}$, $-CH-CH_2\text{-cyclobutyl}$, and $-CH-CH_2\text{-cyclopropyl}$, wherein any of the furanyl, phenyl, thiophenyl or thiazolyl is optionally benzofused and optionally substituted with up to two substituents independently selected from fluoro, chloro, bromo, hydroxy and methyl.

In certain embodiments of Formula II, R^6 is $-C(O)-[CH_2]_{0-1}-R^9$; and R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and C_1-C_4 alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 hydroxyalkyl. In one aspect of these embodiments, R^9 is selected from phenyl, pyridinyl, oxazolyl, pyrazinyl, pyrimidinyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyranyl, $-OCH_3$, and C_1-C_4 alkyl, wherein any phenyl, pyridinyl, oxazolyl, pyrazinyl, or pyrimidinyl in R^9 is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, CF_3 , hydroxy, and $-CH_2OH$.

In certain embodiments of Formula II, each R^7 is independently selected from methyl and hydrogen.

In certain embodiments, the invention provides a compound of Formula IIa:



or a pharmaceutically acceptable salt thereof, wherein:

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R^1 is selected from $-O-$, $-NH-$ and $-N(C_1-C_4 \text{ alkyl-OH})-$;

R^2 is selected from $*-C(H)(R^{10})-(CH_2)_{2-4}-N(H)-C(O)-(C(R^{11}))_{2-5}-$, $*-C(H)(R^{10})-(CH_2)_{4-8}-$, $*-C(H)(R^{10})-(CH_2)_{2-4}-(1,4\text{-phenylene})-N(H)-C(O)-(C(R^{11}))_{2-3}-$, and $*-C(H)(R^{10})-(CH_2)_{2-4}-(1,4\text{-phenylene})-$; wherein:

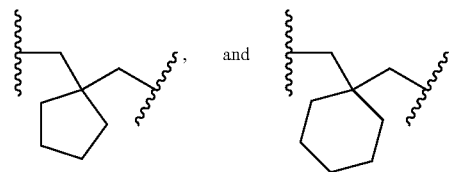
R^{10} is selected from hydrogen, $-C(O)-O-C_1-C_4 \text{ alkyl}$, and $-C(O)-OH$;

each R^{11} is independently selected from hydrogen, benzyl, C_1-C_4 alkyl and C_1-C_4 hydroxyalkyl;

no more than two R^{11} are other than hydrogen;

one methylene unit in a specified $-(CH_2)_{2-4}$ or $-(CH_2)_{4-8}$ portion of R^2 is optionally replaced with $-N(R^7)$; and “*” represents a terminus of R^2 bound to R^1 ;

R^3 is selected from $-(CH_2)_3-$, $-CH_2-C(CH_3)_2-CH_2-$, CH_2- ,



R^4 is selected from $-(CH_2)_4-$, and $-CH_2-(1,4\text{-phenylene})-$.

R^5 is selected from $-CH-(C_1-C_4 \text{ alkyl})$, $-CH-CH_2\text{-aryl}$, $-CH-CH_2\text{-heteroaryl}$, $-CH-CH_2\text{-cycloalkyl}$, and $-CH\text{-cycloalkyl}$, wherein the aryl or heteroaryl is optionally substituted with up to two substituents independently selected from halo, C_1-C_4 alkyl, and phenyl; and

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl;

R^9 is selected from aryl, heteroaryl, cycloalkyl, saturated heterocyclyl, and C_1-C_4 alkyl, wherein R^9 is optionally substituted with up to 2 substituents independently selected from halo, C_1-C_4 alkyl, C_1-C_4 haloalkyl, hydroxy, C_1-C_4 alkoxy, and C_1-C_4 hydroxyalkyl.

II. METHODS OF SYNTHESIZING COMPOUNDS OF THE INVENTION

The compounds of the present invention can be prepared using an iterative peptide coupling procedure as illustrated in following synthetic schemes. Exemplary general synthetic protocols are presented in Schemes 1 through 4. The schemes and accompanying description of synthetic procedures are given for the purpose of illustrating the invention, and should not be construed as limiting the scope or spirit of the invention.

Abbreviations as used herein include O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU); diisopropylethylamine (DIPEA); dimethyl-

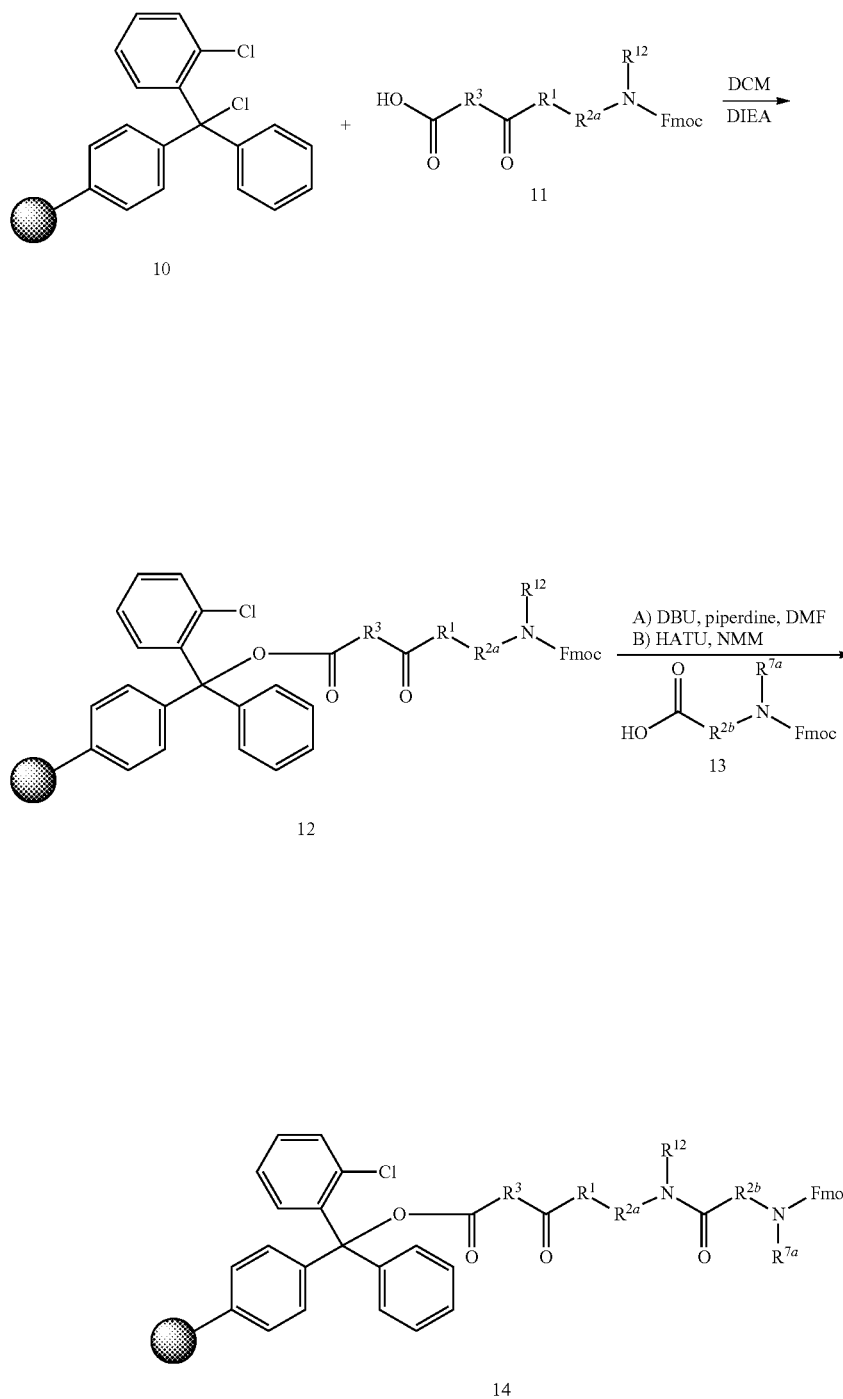
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formamide (DMF); 9-fluorenylmethoxycarbonyl (Fmoc); methanol (MeOH); methylene chloride (DCM); tert-butoxycarbonyl (Boc); tert-butyl (tBu); tetrahydrofuran (THF); trifluoroacetic acid (TFA); 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU); N-methylmorpholine (NMM); 1-hydroxy-7-azabenzotriazole (HOAt); phenyl (Ph); trifluoroacetic acid (TFA); triethylamine (Et₃N); petroleum ether (PE); ethyl

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acetate (EA); acetic acid (AcOH); diethyl ether (Et₂O); Boc anhydride ((Boc)₂O); dimethylsulfoxide (DMSO); diisopropylethylamine (DIEA); N-bromosuccinimide (NBS); trityl chloride (TrtCl); triphenyl phosphate (PPh₃); (9H-fluoren-9-yl)methyl (2,5-dioxopyrrolidin-1-yl) carbonate (Fmoc-Osu); room temperature (r.t. or RT); and thin-layer chromatography (TLC).

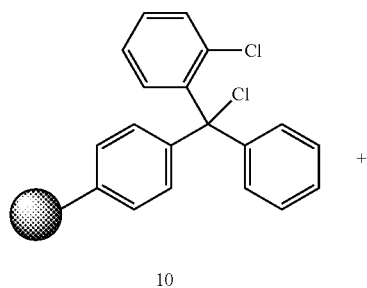
SCHEME 1.



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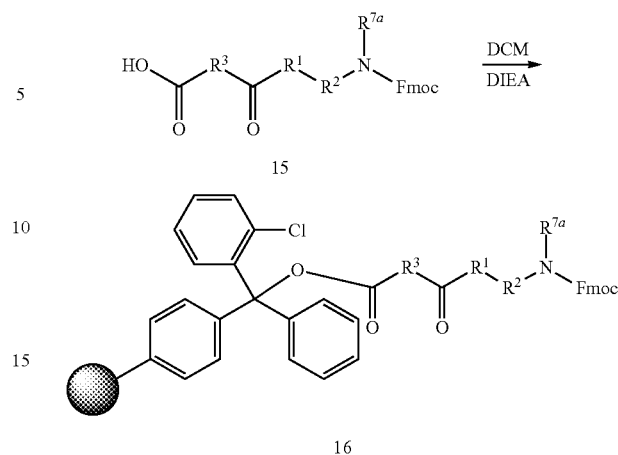
Scheme 1 depicts a general synthesis method for an intermediate to compounds of Formula I, wherein R^2 is $^*\text{—CH}(R^{10})\text{—X—CH}(R^{11})\text{—C(O)—CH}(R^{11})\text{—(CH}_2\text{)}_{0-2}\text{—}$, as defined for Formula I. In Scheme 1, R^{2a} represents the $^*\text{—CH}(R^{10})\text{—X—CH}(R^{11})\text{—}$ terminal portion of R^2 , and R^{2b} represents the $\text{—CH}(R^{11})\text{—(CH}_2\text{)}_{0-2}\text{—}$ terminal portion of R^2 . A 2-chloro-trityl chloride resin 10 is combined with an appropriate protected alkylamino acetic acid 11 in DCM to form resin 12. Resin 12 is then deprotected with DBU and piperidine in DMF and then coupled to a protected amino acid 13 using HATU and NMM to produce resin 14, which is further coupled according to Scheme 3, below.

SCHEME 2.



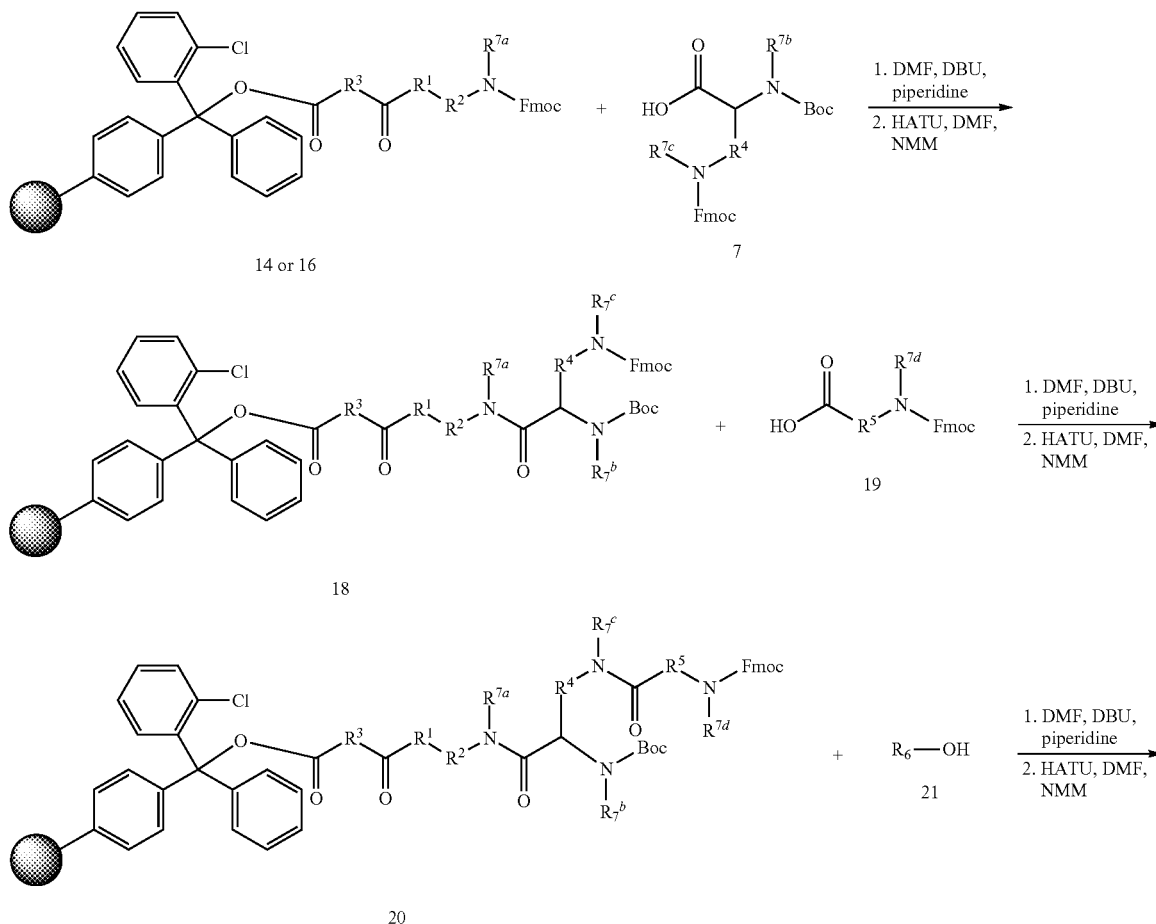
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Scheme 2 depicts a general synthesis method for an intermediate to compounds of Formula I, wherein R^2 is $^*\text{—CH}(R^{10})\text{—Z—}$. A 2-chloro-trityl chloride resin 10 is combined with an appropriate protected alkylamino acetic acid 15 in DCM to form resin 16, which is further coupled according to Scheme 3, below.

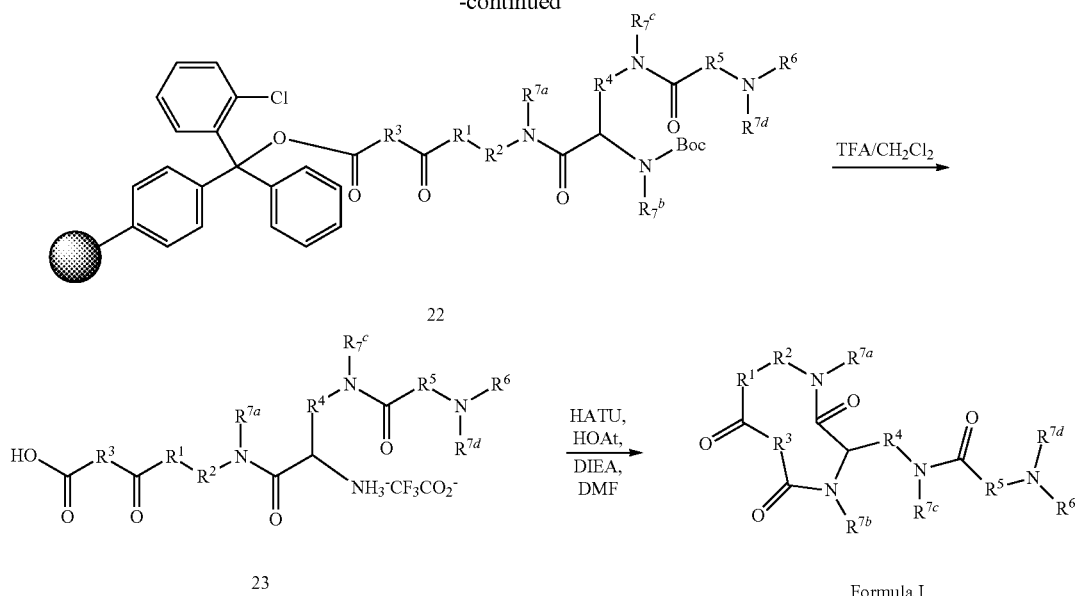
SCHEME 3.



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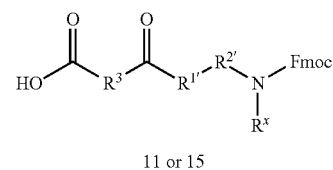
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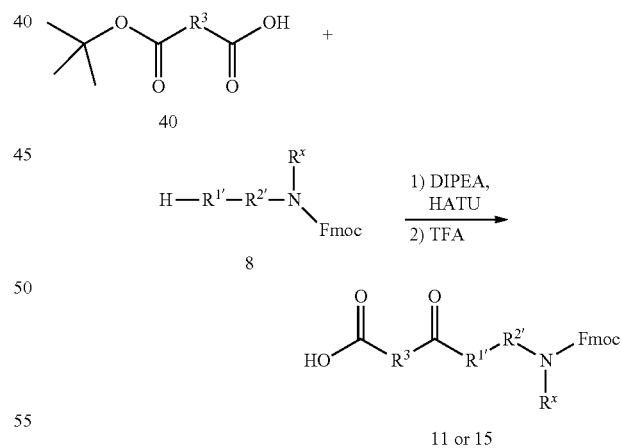


Scheme 3 depicts a general synthesis for compounds of Formula I, starting with intermediate 14 from Scheme 1 or intermediate 16 from Scheme 2. The structures of intermediates 14 and 16 are shown in the scheme for convenience. Each R^7 depicted in Scheme 3 is independently selected from hydrogen and C_1 - C_4 alkyl. Intermediate 14 or intermediate 16 is deprotected with DBU and piperidine in DMF and then coupled to the appropriate N,N' -orthogonally-protected diamino acid 17. The Fmoc group of 17 is removed again with DBU and piperidine in DMF and the resulting deprotected resin is coupled to amino acid 19. The deprotection/coupling process is repeated to add acid 21. Reaction of compound 22 with TFA/ CH_2Cl_2 removes the Boc protecting group and hydrolyzes the ester bond to the resin to form intermediate 23, which is cyclized using HATU, HOAt, DIEA and DMF to form a compound of Formula I.

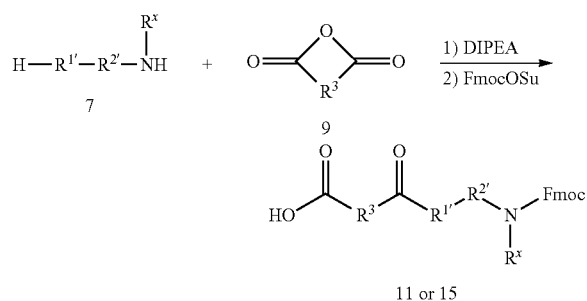
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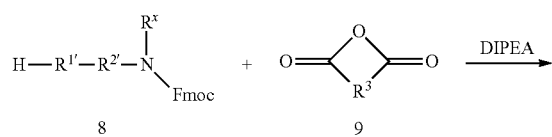
SCHEME 4C



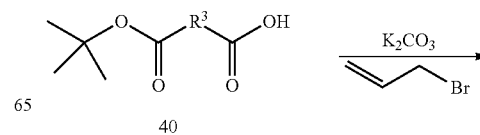
SCHEME 4A

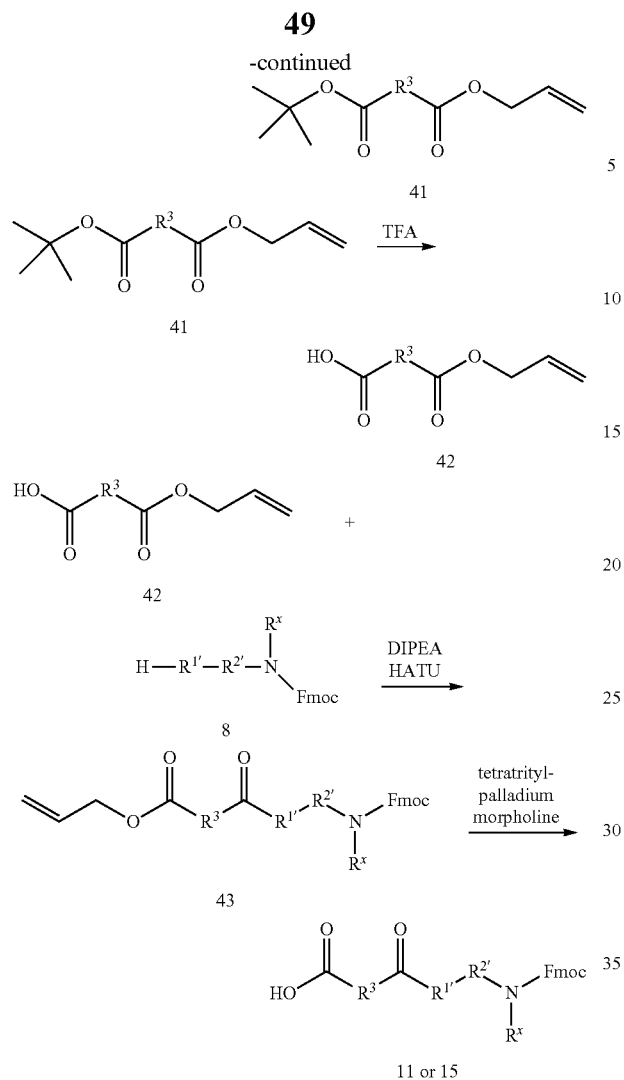


SCHEME 4B



SCHEME 4D

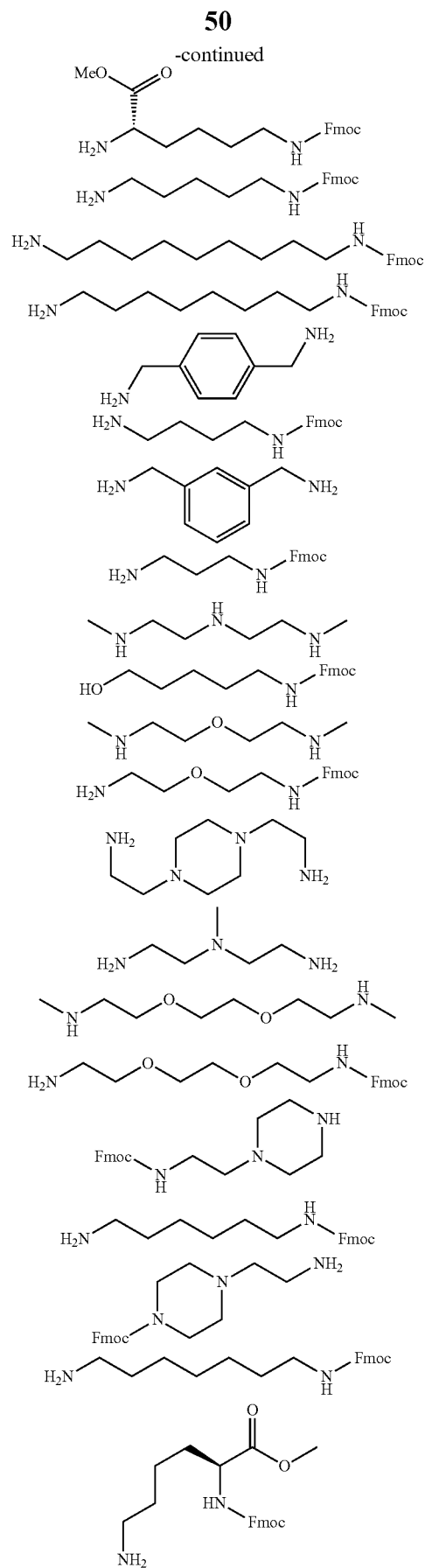
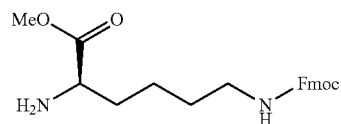




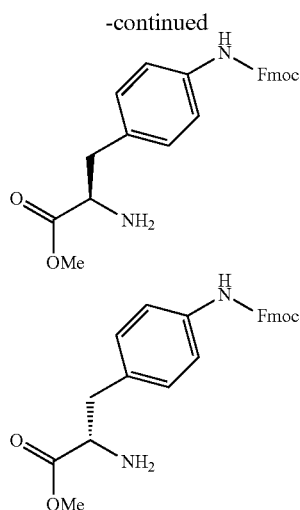
Schemes 4A and 4B depict the synthesis of intermediate 11 or 15 when R^3 is symmetrical. In these schemes, $R^{1'}$ is $-\text{N}(\text{C}_0\text{-C}_3 \text{ alkylene-Q})-$. When R^2 in a compound of Formula I is $^*\text{-CH}(\text{R}^{10})\text{-Z-}$, $R^{2'}$ is $^*\text{-CH}(\text{R}^{10})\text{-Z-}$ and R^x is R^{7a} . When R^2 is $^*\text{-CH}(\text{R}^{10})\text{-X-CH}(\text{R}^{10})\text{-N}(\text{R}^{12})\text{-C}(\text{O})\text{-CH}(\text{R}^{11})\text{-(CH}_2\text{)}_{0-2}\text{-}$, R^{2a} represents the $^*\text{-CH}(\text{R}^{10})\text{-X-CH}(\text{R}^{10})\text{-}$ portion of R^2 and R^x is R^{12} . Scheme 4A was utilized when $\text{H-R}^{1'}\text{-R}^{2'}\text{-NH}(\text{R}^x)\text{-}$ was a symmetrical moiety. Otherwise, Scheme 4B was utilized.

In Scheme 4A, amine reagent 7 is combined with the dioxo cyclic reagent 9 in the presence of DIPEA. The resulting amine is then protected by reaction with FmocOSu to produce intermediate 11 or 15. In Scheme 4B, protected amine 8 is reacted with the dioxo cyclic reagent 9 in the presence of DIPEA to produce intermediate 11 or 15.

A wide variety of reagents 7 and 8 are commercially available, including the following:

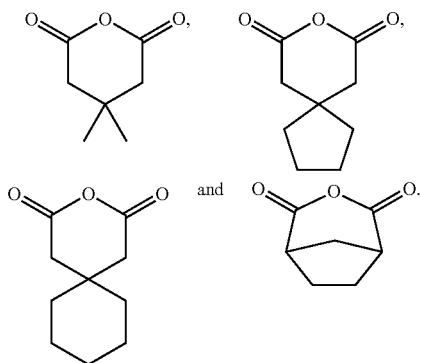


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If additional or alternate protection of reactive groups in such commercially available reagents is required (Fmoc and/or Boc protection; Boc deprotection, methyl esterification), it may be achieved by standard protection protocols well known in the art.

Similarly, a variety of reagents 9 are commercially available including,



Schemes 4C and 4D depict the synthesis of intermediate 11 or 15 when R^3 is asymmetrical. In these schemes, $R^{1'}$ is $-\text{N}(\text{C}_0\text{-C}_3 \text{ alkylene-Q})-$. When R^2 in a compound of Formula I is $^*\text{-CH}(\text{R}^{10})\text{-Z-}$, $R^{2'}$ is $^*\text{-CH}(\text{R}^{10})\text{-Z-}$ and R^x is R^{7a} . When R^2 is $^*\text{-CH}(\text{R}^{10})\text{-X-CH}(\text{R}^{10})\text{-N}(\text{R}^{12})\text{-C}(\text{O})\text{-CH}(\text{R}^{11})\text{-(CH}_2\text{)}_{0-2}\text{-}$, R^{2a} represents the $^*\text{-CH}(\text{R}^{10})\text{-X-CH}(\text{R}^{10})\text{-}$ portion of R^2 and R^x is R^{12} .

In Scheme 4C, protected amine 8 is reacted with carboxylic acid 40 in the presence of DIPEA and HATU, followed by treatment with TFA to produce intermediate 11 or 15.

In Scheme 4D, carboxylic acid 40 is converted to allyloxy-carbonyl carboxylic acid 41 by reaction with 3-bromopropene and K_2CO_3 . The allyloxy-carbonyl carboxylic acid 41 is then reacted with TFA to produce 42, which is then reacted with amine 8 in the presence of DIPEA and HATU to produce allyl intermediate 43. Intermediate 43 is then converted to intermediate 11 or 15 by treatment with tetratritylpalladium and morpholine.

Different t-butyl protected carboxylic acids 40 can be synthesized by reacting an appropriate alkyl carboxylic acid or cycloalkyl carboxylic acid with tert-butyl acrylate. This is shown in more detail in the Examples.

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Combinations of substituents and variables contemplated by the present invention are only those that result in the formation of compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

III. THERAPEUTIC APPLICATIONS

The compounds and pharmaceutical compositions of the present invention are useful in treating or preventing any disease or condition that is mediated directly or indirectly by IL-17. Such diseases include inflammatory diseases and conditions, proliferative diseases (e.g., cancer), autoimmune diseases and other disease described herein.

Increased levels of IL-17 (i.e., IL-17A) have been associated with several conditions including airway inflammation, rheumatoid arthritis (RA), osteoarthritis, bone erosion, intraperitoneal abscesses and adhesions, inflammatory bowel disorder (IBD), allograft rejection, psoriasis, psoriatic arthritis, ankylosing spondylitis, certain types of cancer, angiogenesis, atherosclerosis and multiple sclerosis (MS). Both IL-17 and IL-17R are upregulated in the synovial tissue of RA patients. IL-17 exerts its role in pathogenesis of RA through IL-1 β and TNF- α dependent and independent pathways. IL-17 stimulates secretion of other cytokines and chemokines, e.g., TNF- α , IL-1 β , IL-6, IL-8 and Gro- α . IL-17 directly contributes to disease progression in RA. Injection of IL-17 into the mouse knee promotes joint destruction independently of IL-1 β activity (Ann Rheum Dis 2000, 59:529-32). Anti-IL-1 β antibody has no effect on IL-17 induced inflammation and joint damage (J Immunol 2001, 167:1004-1013). In an SCW-induced murine arthritis model, IL-17 induced inflammatory cell infiltration and proteoglycan depletion in wild-type and IL-1 β knockout and TNF- α knockout mice. IL-17 knockout mice are phenotypically normal in the absence of antigenic challenge, but have markedly reduced arthritis following type II collagen immunization (J Immunol 2003, 171:6173-6177).

Increased levels of IL-17-secreting cells have also been observed in the facet joints of patients suffering from ankylosing spondylitis (H Appel et al., Arthritis Res Therap 2011, 13:R95).

Multiple sclerosis is an autoimmune disease characterized by central nervous system (CNS) inflammation with damage to the myelin sheath surrounding axons. A hallmark of MS is that T cells infiltrate into the CNS. Higher numbers of IL-17 mRNA-expressing blood mono-nuclear cells (MNC) are detected during MS clinical exacerbation compared to remission (Multiple Sclerosis, 5:101-104, 1999). Furthermore, experimental autoimmune encephalomyelitis ("EAE"), a preclinical animal model for MS is significantly suppressed in IL-17 knockout mice.

In one embodiment, the invention provides a method for the treatment or prevention of a condition including, but not limited to, airway inflammation, ankylosing spondylitis, asthma, RA (including juvenile RA), osteoarthritis, bone erosion, intraperitoneal abscesses and adhesions, IBD, Crohn's disease, allograft rejection, psoriasis, psoriatic arthritis, certain types of cancer, angiogenesis, atherosclerosis and MS, as well as other inflammatory disorders, conditions, diseases or states including without limit: erythematous, response to allergen exposure, *Helicobacter pylori* associated gastritis, bronchial asthma, allograft rejection (e.g., renal), systemic

lupus erythematosus and lupus nephritis. The method comprises the step of administering to a subject in need thereof an amount of a compound or composition of the invention effective to treat the condition.

In another embodiment, the invention provides a method for the treatment or prevention of a condition including, but not limited to, Behcet's disease, ulcerative colitis, Wegener's granulomatosis, sarcoidosis, systemic sclerosis, insulin-dependent diabetes mellitus, septic shock syndrome, Alzheimer's disease, an inflammatory eye disease, and uveitis.

In a more specific embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention may be useful for the treatment or prevention of a condition selected from RA, airway inflammation, MS, psoriasis, psoriatic arthritis, and ankylosing spondylitis. More specifically, the condition is RA.

The use of the compounds of the present invention for treating or preventing of at least one of the aforementioned disorders in which IL-17 activity is detrimental or which benefits for decreased levels of bioactive IL-17 is contemplated herein. Additionally, the use of a compound of the present invention for use in the manufacture of a medicament for the treatment of at least one of the aforementioned disorders is contemplated.

In another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of IL-17; and b) if the patient does have an elevated level of IL-17, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition.

In still another aspect, the invention provides a method of treating a patient suffering from a disease or condition associated with elevated levels of IL-17 comprising the steps of: a) determining whether the patient has an elevated level of one or more IL-17-induced chemokine or effector; and b) if the patient does have an elevated level of the one or more IL-17 chemokine or effector, administering to the patient an effective amount of a compound of Formula I for a time sufficient to treat the disease or condition. In certain aspects the IL-17 chemokine or effector is one or more of IL-6, IL-8, G-CSF, TNF- α , IL-1 β , PGE2, and IFN- γ .

Methods for determining the levels of IL-17 or any of its chemokines or effectors in a patient are well-known in the art. Typically, a tissue or biological fluid sample is obtained from the patient and is subject to ELISA with commercially available antibodies or kits (e.g., Quantikine IL-17 ELISA; R&D Systems, Abington, UK). Commercially available antibodies and kits are available for IL-6, IL-8, G-CSF, TNF- α , IL-1 β , PGE2, and IFN- γ .

The invention also provides for combination therapy of a macrocyclic compound described herein and a second therapeutic agent. "Combination therapy" (or "co-therapy") includes the administration of a macrocyclic compound described herein and at least a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents. Administration of these therapeutic agents in combination typically is carried out over a defined time period (usually minutes, hours, days or weeks depending upon the combination selected).

Combination therapy is intended to embrace administration of these therapeutic agents in a sequential manner, that is,

wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents, in a substantially simultaneous manner. Substantially simultaneous administration can be accomplished, for example, by administering to the subject a single dosage form having a fixed ratio of each therapeutic agent or in multiple, single dosage forms for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. Combination therapy also can embrace the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (e.g., surgery or radiation treatment.) Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

Accordingly, in certain instances, the method further comprises administering a therapeutically effective amount of an anti-inflammatory agent. In certain instances, the anti-inflammatory agent is a salicylate, diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac, indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, piroxicam, droxicam, lornoxicam, meloxicam, tenoxicam, ibuprofen, alminoprofen, carprofen, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuproxam, indoprofen, ketorolac, loxoprofen, naproxen, oxaprozin, piroprofen, suprofen, tiaprofenic acid, mefenamic acid, flufenamic acid, meclofenamic acid, tolfenamic acid, phenylbutazone, ampyrone, azapropazone, clofezone, kebutzone, metamizole, mofebutazone, oxyphenbutazone, phenazone, phenylbutazone, sulfapyrazone, celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, valdecoxib, prednisone, methylprednisolone, hydrocortisone, or budesonide.

In certain instances, the method further comprises administering a therapeutically effective amount of an agent for treating multiple sclerosis. In certain instances, the agent for treating multiple sclerosis is interferon beta-2, interferon beta-1, glatiramer, natalizumab, or mitoxantrone.

In certain instances, the method further comprises administering infliximab, etanercept, adalimumab, or certolizumab pegol.

In certain instances, the method is designed to treat rheumatoid arthritis and further comprises the step of administering to the patient in need thereof a therapeutically effective amount of an agent selected from the group consisting of a salicylate, diclofenac, aceclofenac, acemetacin, alclofenac, bromfenac, etodolac, indometacin, nabumetone, oxametacin, proglumetacin, sulindac, tolmetin, piroxicam, droxicam, lornoxicam, meloxicam, tenoxicam, ibuprofen, alminoprofen, carprofen, dexibuprofen, dexketoprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuproxam, indoprofen,

ketorolac, loxoprofen, naproxen, oxaprozin, pirofen, suprofen, tiaprofenic acid, mefenamic acid, flufenamic acid, meclofenamic acid, tolfenamic acid, phenylbutazone, ampyrone, azapropazone, clofezone, kebutzone, metamizole, mofebutazone, phenazone, sulfinpyrazone, celecoxib, etoricoxib, lumiracoxib, parecoxib, prednisone, methylprednisolone, hydrocortisone, and budesonide.

IV. PHARMACEUTICAL COMPOSITIONS AND DOSING

The invention also provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the macrocyclic compounds of Formula I, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents, and optionally, one or more additional therapeutic agents described above. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or

polyanhydrides; and (22) other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, troches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose,

glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; (7) wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as croscopolidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and

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suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

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A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, oral, intravenous, intracerebroventricular and subcutaneous doses of the compounds of this invention for a patient will range from about 0.01 to about 50 mg per kilogram of body weight per day.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain aspects of the invention, dosing is one administration per day.

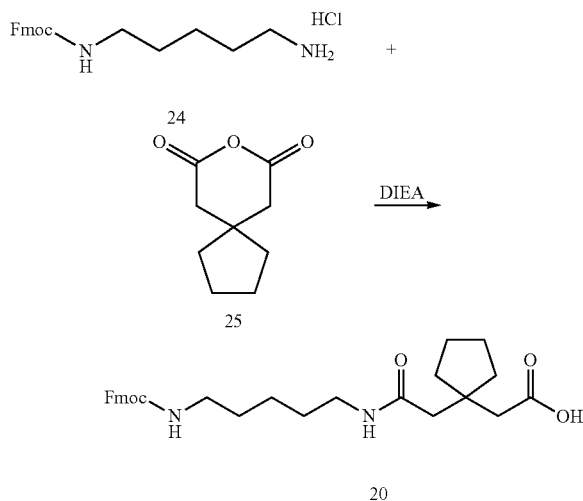
While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical formulation (composition).

EXAMPLES

The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example 1

Synthesis of 2-(1-(2-(4-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-2-oxoethyl)cyclopentyl)acetic Acid (Intermediate 20)

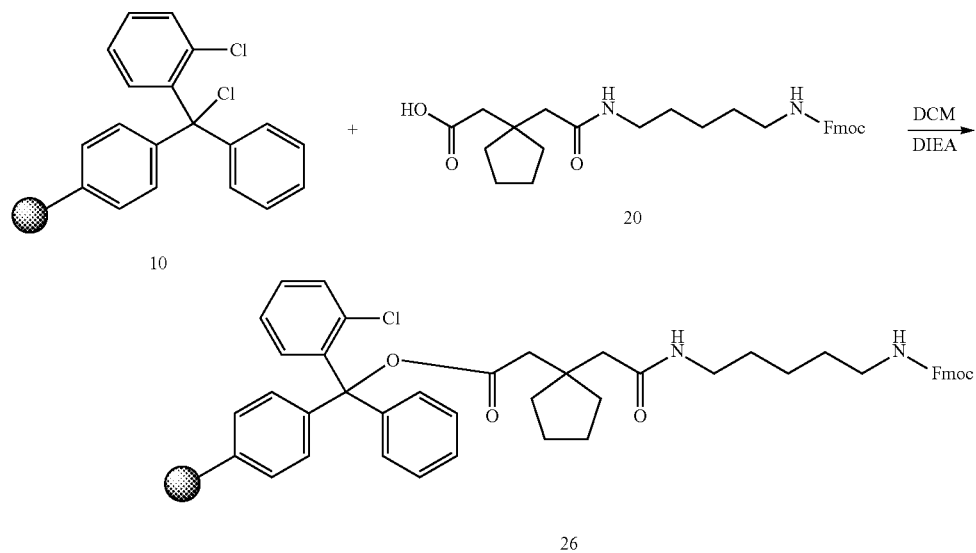


(9H-fluoren-9-yl)methyl (5-aminopentyl)carbamate hydrochloride (24; 3.2 g, 8.9 mmol) and N-ethyl-N-isopropylpropan-2-amine (8.7 mL, 49.5 mmol) were dissolved in DMF (40 mL) followed by addition of 8-oxaspiro[4.5]decan-7,9-dione (25; 5 g, 29.7 mmol). The mixture was agitated for 1 hr followed by evaporation of volatiles. The crude product was purified directly on a Biotage purification system using 45%-75% acetonitrile/water. After evaporation of volatiles and lyophilization, a white powder was isolated consistent with desired product 20 (1.5 g, 3.0 mmol, 34%).

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Example 2

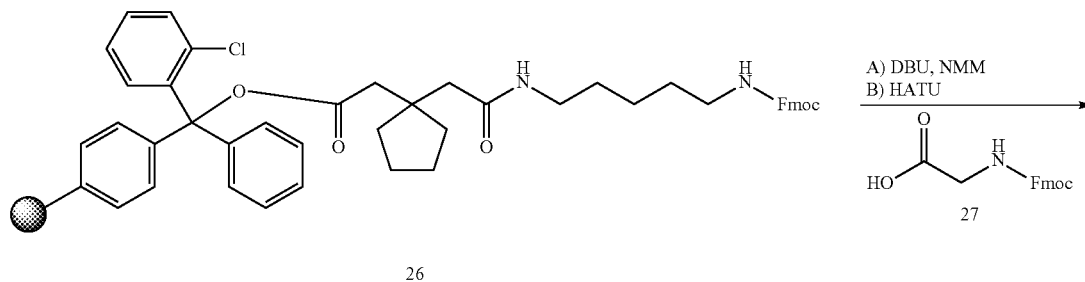
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Synthesis of Compound 159



2-Chloro-trityl chloride resin (10; 0.58 g, 0.70 mmol) was swelled in DCM (5 mL) for 10 min, then filtered, and washed with DCM (5 mL). 2-(1-(2-(4-(((9H-fluoren-9-yl)methoxy)carbonylamino)butylamino)-2-oxoethyl)cyclopentyl)acetic acid (20; 0.335 g, 0.700 mmol) and N-ethyl-N-isopropylpropan-2-amine (0.610 mL, 3.50 mmol) was dissolved in DCM

(30 mL). The resulting solution was added to the swelled resin and agitated for 2 hours. The resin was then washed with 85:10:5 DCM:MeOH:DIPEA (5 mL×3); DCM (5 mL×3), DMF (5 mL×3), and DCM (5 mL×3). After flushing with argon and drying under vacuum, resin 26 (0.99 g) was obtained.

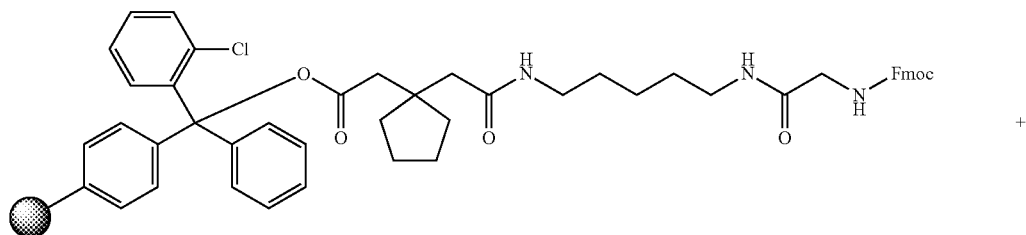


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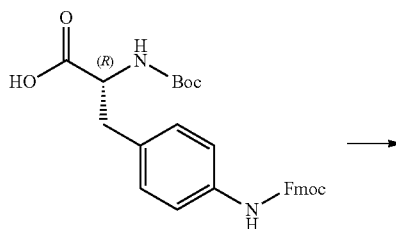
Resin 26 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N₂ every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N₂ every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Fmoc-glycine (27; 0.1 M

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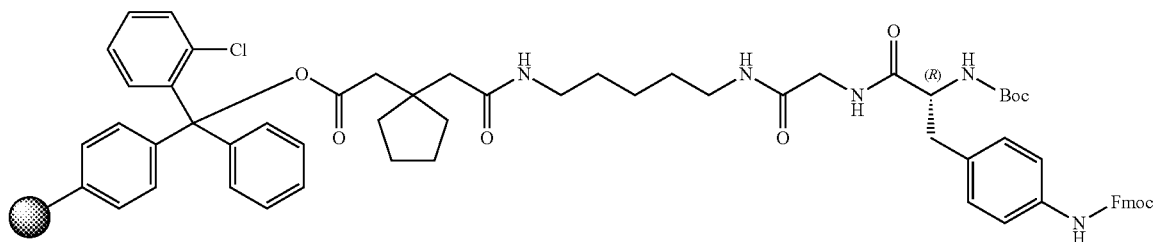
solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2 M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 28 was washed six times with DMF (2 mL×30 sec).



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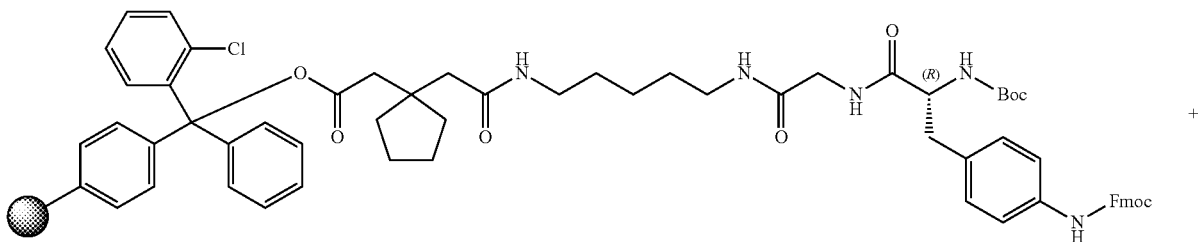
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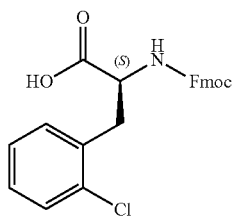
Resin 28 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N₂ every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N₂ every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). (R)-3-(4-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)-phenyl)-2-((tert-butoxycar-

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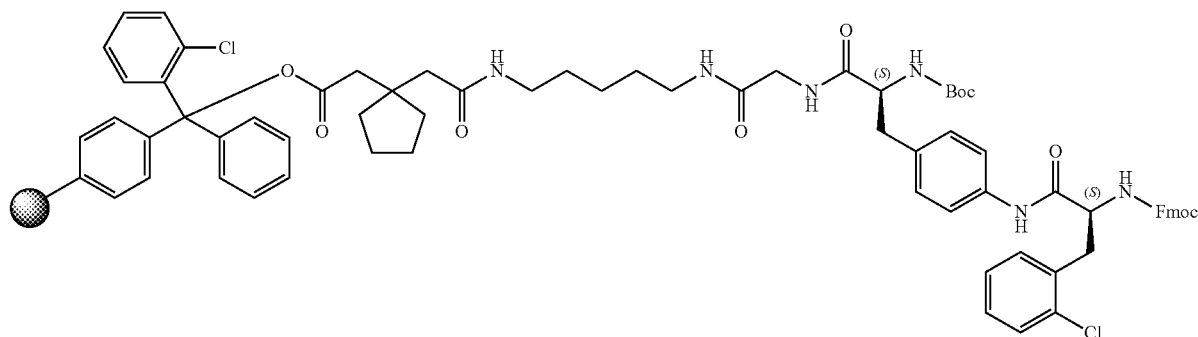
bonyl)amino)propanoic acid 29; (0.1 M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 30 was washed six times with DMF (2 mL×30 sec).



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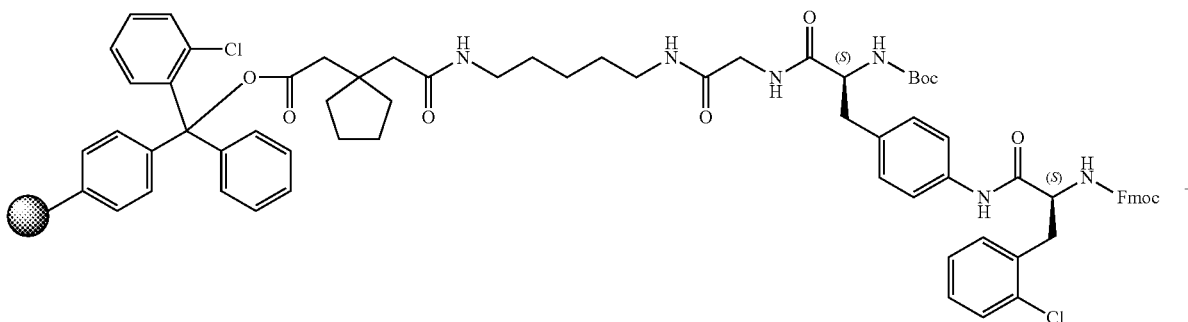
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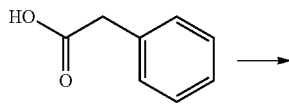
Resin 30 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N₂ every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N₂ every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Fmoc-2-chlorophenyl-

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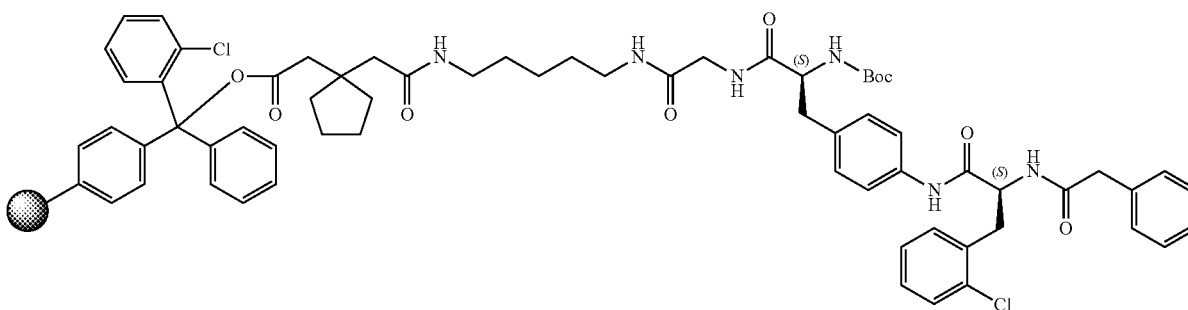
lanine (31; 0.1 M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), followed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 5 hr. The reagents were drained from the reaction vessel, and the resin 32 was washed six times with DMF (2 mL×30 sec).



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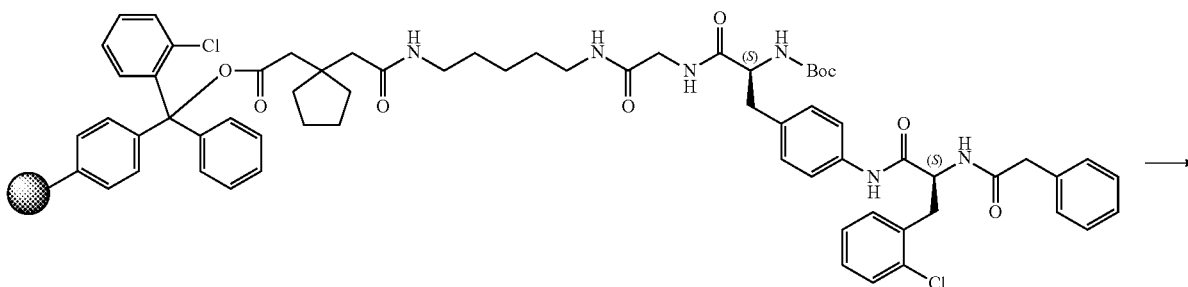
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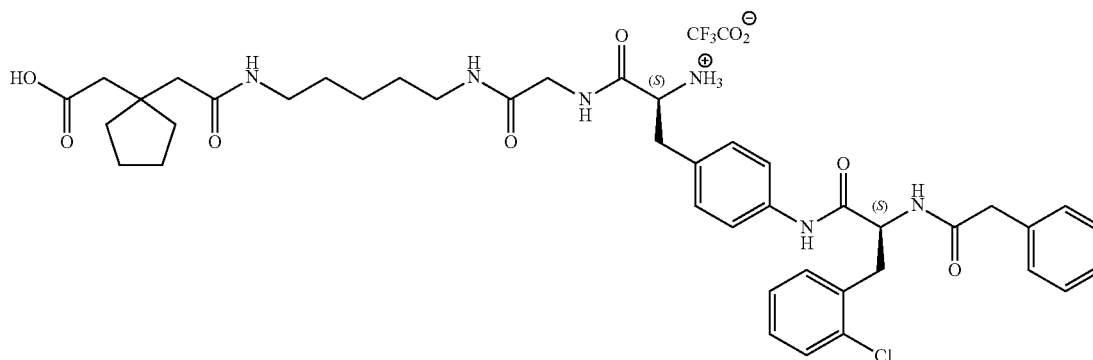
Resin 32 (0.075 mmol, 125 mg) was suspended in DMF (2 mL×5 min) and mixed with a stream of N₂ every 30 seconds. The Fmoc group was removed from the resin-supported building block by mixing the resin twice with a solution of 2% DBU, 2% piperidine in DMF (2 mL×5 min) while agitating with a stream of N₂ every 30 seconds. The resin was washed six times with DMF (2 mL×30 sec). Phenylacetic acid (33; 0.1M solution in DMF, 2.5 mL, 3.3 equiv, 0.25 mmol), fol-

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lowed by HATU (0.2M solution in DMF, 1.15 mL, 3.1 equiv, 0.23 mmol) and N-methyl morpholine (1.0 M in DMF, 0.5 mL, 6.7 equiv, 0.5 mmol) were added to the resin. The reaction mixture was agitated by a stream of nitrogen for 30 min. The reagents were drained from the reaction vessel, and the resin 34 was washed six times with DMF (2 mL×30 sec), and six times with DCM (2 mL×30 sec).

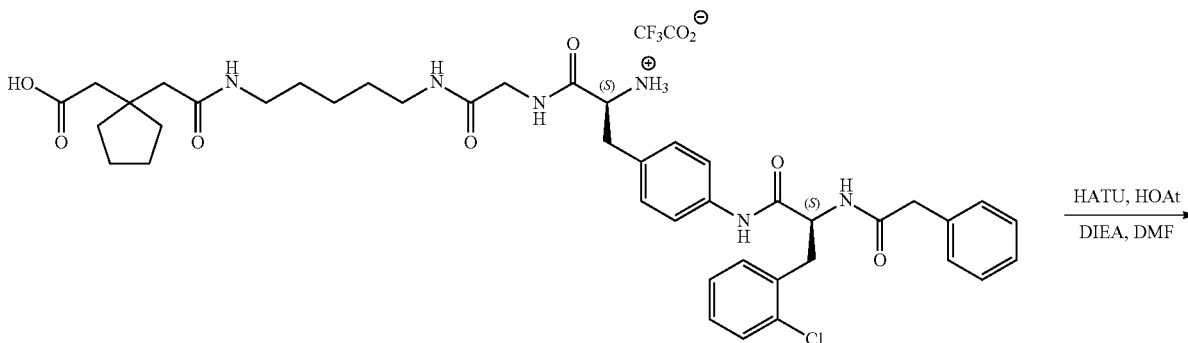


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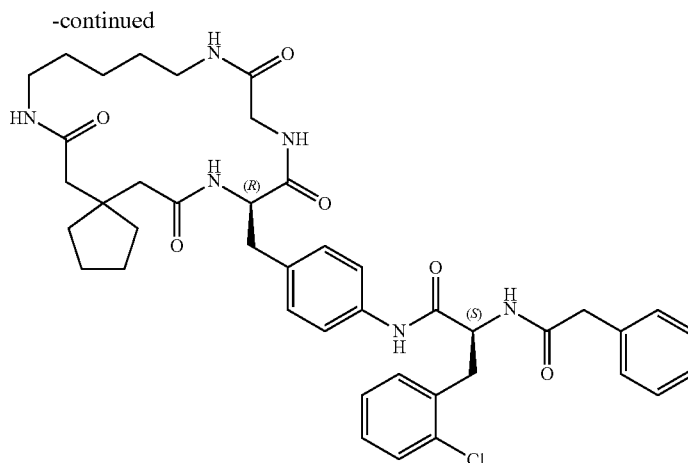
Resin 34 (0.075 mmol, 125 mg) was treated with 5% TFA in CH₂Cl₂ (4 mL×5 min) then washed with DCM (4 mL). Treatment with TFA was repeated two more times and the fractions combined. TFA (1 mL) was added and solvent was removed by evaporation using a Genevac EZ2.2 evaporator. The crude reaction mixture 35 was carried on to the next reaction.



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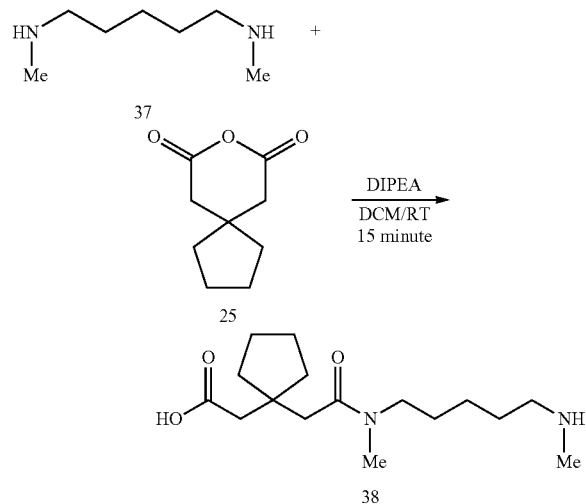


Compound 159

Crude reaction product 35 (0.075 mmol) and DIEA (0.13 mL, 10 equiv) were dissolved in DMF (5 mL). This solution was added to a solution containing HATU (34 mg, 0.090 mmol, 1.2 equiv) and HOAt (12 mg, 0.090 mmol, 1.2 equiv) dissolved in DMF (30 mL). After 30 minutes, the volatiles were evaporated on a Genevac EZ2.2 evaporator at 50° C. The resultant crude mixture was dissolved in DMSO and purified on a Waters HPLC. Evaporation of volatiles followed by lyophilization resulted in Compound 159 (32 mg, 0.042 mmol, 56% yield) as a white powder.

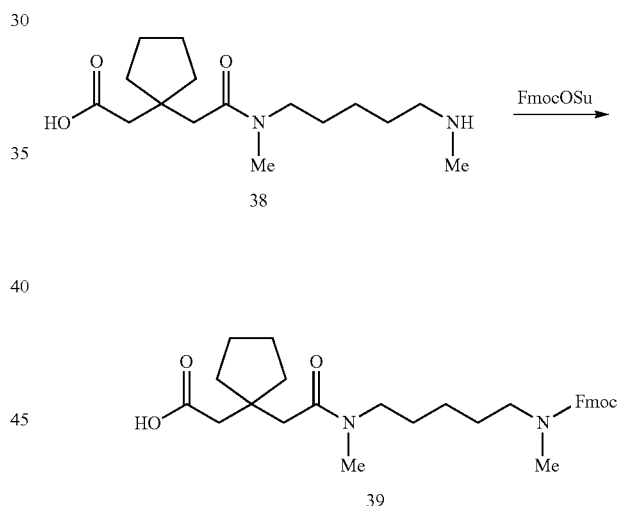
Example 3

Synthesis of 2-(1-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (Intermediate 39)



A 250 mL flask with magnetic stirring bar is charged with 1,5-di(methylamino)pentane (37; 1.0 g, 7.7 mmol), followed by 120 mL of dichloromethane. The mixture is stirred at room temperature for 5 minutes followed by addition of 8-oxazapiridine-2,5-dione (25; 1.29 g, 7.7 mmol) and diisopropylethylamine (1.34 mL, 30.8 mmol). The solution is allowed to stir for 15 minutes and the resulting 2-(1-(2-(methyl(5-(methylamino)pentyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 38 is used directly for the next reaction without any purification.

[4.5]decane-7,9-dione (25; 1.29 g, 7.7 mmol) and diisopropylethylamine (1.34 mL, 30.8 mmol). The solution is allowed to stir for 15 minutes and the resulting 2-(1-(2-(methyl(5-(methylamino)pentyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 38 is used directly for the next reaction without any purification.



To the above solution is introduced (9H-fluoren-9-yl)methyl (2,5-dioxopyrrolidin-1-yl) carbonate (3.1 g, 9.2 mmol). The solution is stirred for 15 minutes. The resulting mixture is treated with 1.2N HCl solution and the pH adjusted to 3.0. The organic layer is separated and dried with Na₂SO₄. The crude product is purified by silica gel chromatography (acetonitrile/methylene chloride: 0-30%) providing a white powder (1.8 g, 3.4 mmol, 45% from diamine) consistent with desired product 39. The desired product 39 can be utilized in general Scheme 1 as a version of intermediate 11, or in general Scheme 2, as a version of intermediate 15.

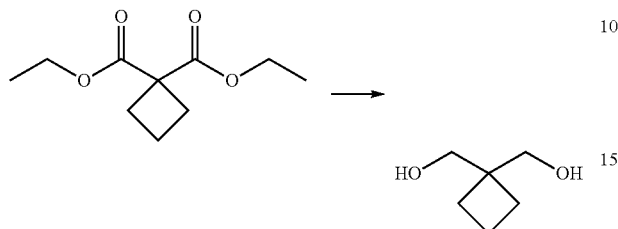
Other compounds of Formula I were made by a similar process as described above with the appropriate substitution for one or more of reagents 20, 24, 25, 27, 29, 31, 33 and/or 37. Those of ordinary skill in the art should make reference to Schemes 1-4 herein, commercially available reagents/com-

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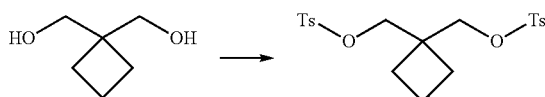
pounds and standard organic chemistry protocols to obtain appropriate substitutions for any of these reagents.

Example 4

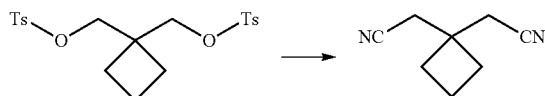
Synthesis of 7-oxaspiro[3.5]nonane-6,8-dione



A solution of diethyl cyclobutane-1,1-dicarboxylate (4.76 ml, 24.97 mmol) in diethyl ether was cooled to 0° C. Aluminum(III) lithium hydride (49.9 ml, 100 mmol) in THF was added over 15 min. The reaction was warmed to room temperature and left to stir for 3 hours. A 20% solution of sodium hydroxide was added followed by diethyl ether. The organic layer was isolated, dried with magnesium sulfate, and concentrated under vacuum. Recovered cyclobutane-1,1-diylmethanol (23.86 mmol, 96% yield) as pure material.

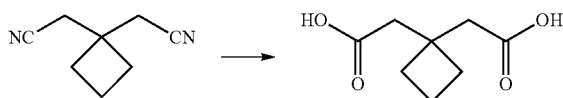


4-methylbenzene-1-sulfonyl chloride (13.79 g, 72.3 mmol) was dissolved in pyridine and cooled to 0° C. Cyclobutane-1,1-diylmethanol (2.8 g, 24.11 mmol) in pyridine was added over 10 min. The mixture was stirred for 2 hours at 0° C. and then for 48 h at room temperature. The material was partitioned between 50 ml DCM and 50 ml water. The aqueous layer was washed with 1× with 50 ml DCM. The organic layers were combined and washed with 50 ml 1.2 M HCl and brine and then dried over MgSO₄, filtered, and concentrated under reduced pressure. The material was then purified on Companion Combiflash using a gradient of 0-10% ethyl acetate in hexanes. The desired fractions were combined and dried down to give cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) (8.72 mmol, 36.2% yield).

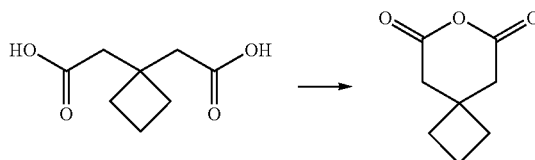


Cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) (3.7 g, 8.72 mmol) was dissolved in 5 ml DMSO. KCN (1.703 g) was added and the mixture stirred overnight at 90° C. The reaction mixture was diluted with water (100 mL) and extracted with dichloromethane (50 mL×3). The organic extracts were combined, washed with brine (50 mL), dried over MgSO₄, and concentrated under vacuum to give 2,2'-(cyclobutane-1,1-diyl)diacetonitrile (8.71 mmol, 100% yield).

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2,2'-(cyclobutane-1,1-diyl)diacetonitrile (1.169 g, 8.71 mmol) was dissolved in 20% KOH, heated to reflux and refluxed for 48 h. Concentrated HCl was added dropwise until solution reached a pH of 1 and the solution was extracted with DCM (3×10 ml). Organic layers were combined and dried over MgSO₄, filtered, and concentrated to give 2,2'-(cyclobutane-1,1-diyl)diacetic acid (4.07 mmol, 46.7% yield).

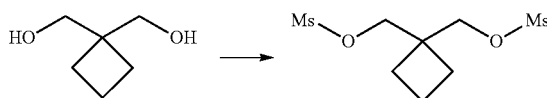


2,2'-(cyclobutane-1,1-diyl)diacetic acid (0.7 g, 4.07 mmol) was dissolved in acetic anhydride (5.75 mL, 61.0 mmol) and refluxed overnight. The solution was cooled to r.t. Acetic anhydride was removed under reduced pressure to give a brown oil, which was then recrystallized by dissolving in ether/hexanes, cooling to 0° C. and collecting crystals by vacuum filtration. The crystals were dried under vacuum overnight producing 7-oxaspiro[3.5]nonane-6,8-dione (2.147 mmol, 52.8% yield) as a light brown solid.

The resulting 7-oxaspiro[3.5]nonane-6,8-dione was used as intermediate 9 in Schemes 4A and 4B set forth previously to produce compounds of the invention having a cyclobutyl glutarate moiety (e.g., Compound Nos. 535 and 536).

Example 5

Synthesis of cyclopropane-1,1-diylbis(methylene)dimethanesulfonate



Cyclopropane-1,1-diylmethanol (0.5 g, 4.90 mmol) was dissolved in DCM (6 ml). Triethylamine (2.73 mL, 19.58 mmol) was added, as was a solution of methanesulfonyl chloride (1.141 mL, 14.69 mmol) in DCM (4 ml) at 0° C. The mixture was stirred for 2 h at room temperature. After 2 h, 1.2N HCl was added, and the aqueous layer removed and washed 3× with DCM. The resulting organic layers were combined with the original layer, dried over MgSO₄, filtered, and concentrated to give 1.31 g crude material. The crude material was washed with hexanes to produce cyclopropane-1,1-diylbis(methylene)dimethanesulfonate (2.323 mmol, 47.4% yield).

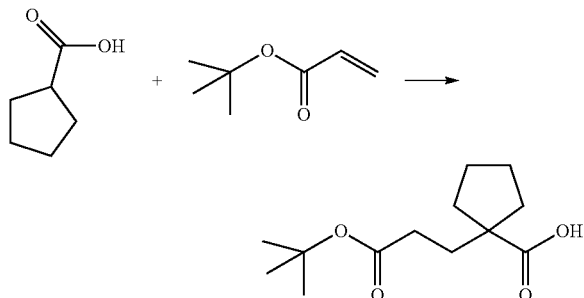
The resulting cyclopropane-1,1-diylbis(methylene)dimethanesulfonate was used in place of cyclobutane-1,1-diylbis(methylene)bis(4-methylbenzenesulfonate) in Example 4 and, following the procedures set forth in Example 4, ultimately produced 6-oxaspiro[2.5]octane-5,7-dione.

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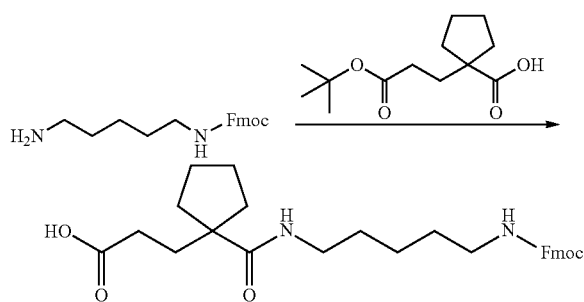
6-oxaspiro[2.5]octane-5,7-dione was used as intermediate 9 in Schemes 4A and 4B set forth previously to produce compounds of the invention having a cyclopropyl glutarate moiety (e.g., Compound No. 554).

Example 6

Synthesis of 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoic Acid



To a 50 ml round-bottomed flask under nitrogen was added lithium diisopropylamide (10.95 mL, 21.90 mmol). The solution was cooled to -20° using a controlled dry ice/acetonitrile bath. Cyclopentanecarboxylic acid (1.187 mL, 10.95 mmol) in dry THF (10 mL) was added over 5 minutes, keeping the temperature at -20° C. The mixture was warmed to room temperature, stirred for one hour, then cooled to -78° C. Tert-butyl acrylate (1.685 mL, 10.95 mmol) in dry THF (10 mL) was added dropwise over 5 min, keeping the temperature at -70° C. After 2 hours at -70° C., the mixture was quickly warmed to 0° C., acidified with 5N HCl, and extracted with hexane. The hexane extract was washed with water and saturated sodium bicarbonate, water, and dried over MgSO_4 , and then recrystallized from hexanes. Recovered 1-(3-tert-butoxy-3-oxopropyl)cyclopentanecarboxylic acid (1.8 g, 7.43 mmol, 67.8% yield).

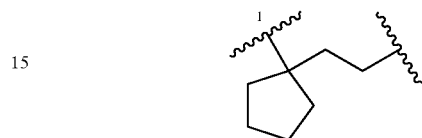


To a solution of (9H-fluoren-9-yl)methyl 5-aminopentylcarbamate (0.683 g, 2.105 mmol) in 15 ml DMF was added HATU (0.800 g, 2.105 mmol), 1-(3-tert-butoxy-3-oxopropyl)cyclopentanecarboxylic acid (0.425 g, 1.754 mmol) in 5 ml DMF, and DIEA (1.532 mL, 8.77 mmol). The solution was stirred for 10 minutes and material purified by HPLC using a gradient of 0-50% acetonitrile in DCM. Solvents were removed under reduced pressure to give 1.2 g crude tert-butyl 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoate. The crude material was dissolved in 20 ml DCM and 10 ml TFA was added to

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remove t-Bu group. Solvent was removed under reduced pressure and material purified by reverse phase chromatography to give 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoic acid (16 mg, 0.032 mmol, 1.852% yield).

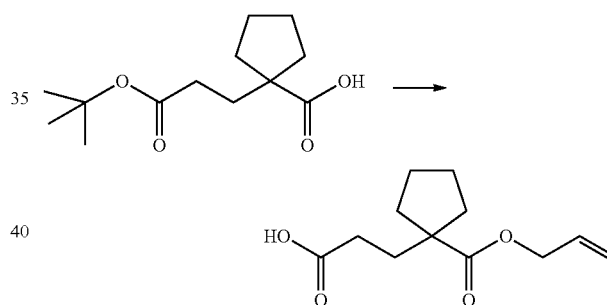
The resulting 3-(1-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylcarbamoyl)cyclopentyl)propanoic acid was employed as intermediate 15 in Scheme 2 to produce compounds of the invention where R^3 is



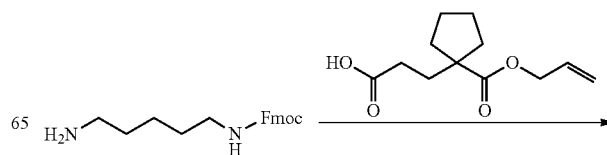
e.g. (Compound 543).

Example 7

Synthesis of 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentane Carboxylic Acid

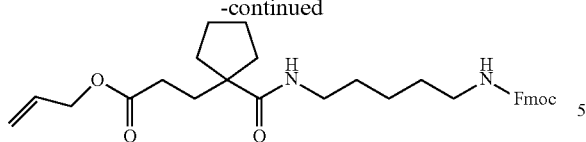


1-(3-tert-butoxy-3-oxopropyl)cyclopentanecarboxylic acid (1.275 g, 5.26 mmol) and 3-bromoprop-1-ene (0.911 mL, 10.52 mmol) were dissolved in 25 mL of acetone. Potassium carbonate (2.55 g, 18.42 mmol) was then added in one portion. The resulting suspension was stirred at reflux for 3 hours. The insoluble inorganic salts were removed by filtration and the reaction mixture was concentrated under reduced pressure to yield crude product. The crude product was dissolved in dichloromethane (10 mL) to which was added TFA (2.5 mL) to remove Boc group. The reaction was stirred for 15 min then the solvent removed under reduced pressure to give crude material (1.04 g, quantitative yield), which was used without further purification.

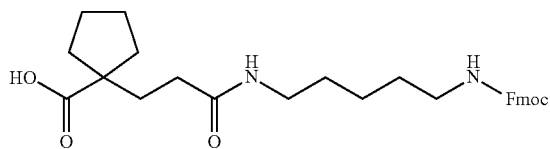
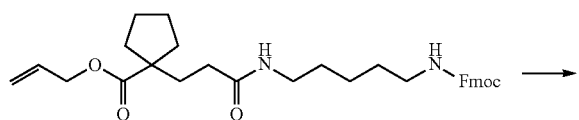


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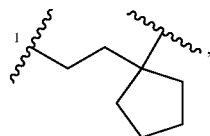


To a solution of 3-(1-(allyloxycarbonyl)cyclopentyl)propanoic acid (1.191 g, 5.26 mmol) in 40 ml DMF was added (9H-fluoren-9-yl)methyl 5-aminopentylcarbamate (2.049 g, 6.32 mmol), DIEA (4.60 mL, 26.3 mmol) and HATU (2.402 g, 6.32 mmol). After stirring for 10 minutes, DMF was removed under reduced pressure. The material was subjected to normal-phase purification using a gradient of 0-100% acetonitrile in DCM. Fractions containing the desired material were combined and solvent removed under reduced pressure to give crude allyl 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylate (360 mg, 0.676 mmol, 12.84% yield) that was used in the next step without further purification.



Allyl 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylate (360 mg, 0.676 mmol) was dissolved in DMF (15 mL) and cooled to 0° C. under nitrogen. Tetratritylpalladium (122 mg, 0.113 mmol) and morpholine (941 mg, 10.8 mmol) were added and the mixture stirred for 2 h. Solvent was removed under reduced pressure and material was purified by reverse-phase chromatography. Recovered 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylic acid (54.4 mg, 0.110 mmol, 16.34% yield).

The resulting 1-(3-(5-(((9H-fluoren-9-yl)methoxy)carbonylamino)pentylamino)-3-oxopropyl)cyclopentanecarboxylic acid was employed as intermediate 15 in Scheme 2 to produce compounds of the invention where R³ is

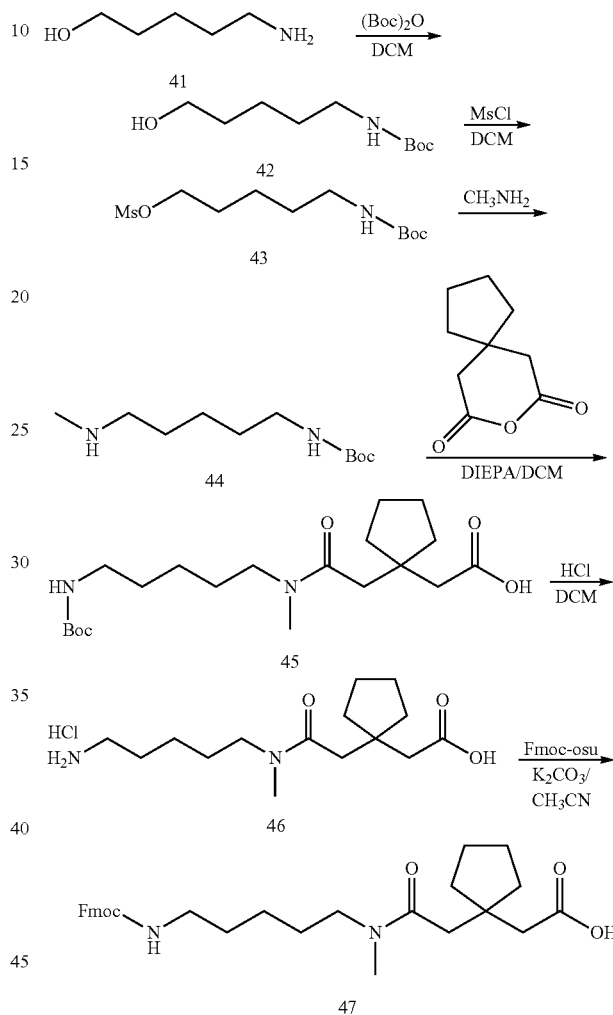


e.g., Compound 561.

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Example 8

Synthesis of 2-(1-(2-((5-(((9H-fluoren-9-yl)methoxy)carbonyl)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (47)



To a solution of 41 (20 g, 194 mmol) in DCM (0.2 L) was added (Boc)₂O dropwise (42.3 g, 194 mmol) under an ice bath. The reaction was stirred at RT over night. Then the mixture solution was extracted with DCM and washed with water. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum to give 42 as an oil (37 g, yield 93.1%). ¹H NMR (300 MHz, CDCl₃) δ: 3.5 (m, 2H), 3.2 (m, 2H), 1.6-1.5 (m, 4H), 1.4-1.3 (m, 11H).

To a solution of 42 (10 g, 49.2 mmol) in DCM (100 mL) and Et₃N (9.9 g, 98.5 mmol) was added methanesulfonyl chloride (6.7 g, 59.1 mmol) in portions over 20 minutes under an ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give 43 (12 g, yield: 86.9%). ¹H NMR (300 MHz, CDCl₃) δ: 4.0 (m, 2H), 3.1-3.0 (m, 3H), 3.2-3.1 (m, 2H), 1.6-1.5 (m, 4H), 1.4-1.3 (m, 11H).

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To a solution of 43 (12 g, 42 mmol) in 1,4-dioxane (100 mL) was added CH_3NH_2 aqueous slowly (30%, 100 mL) at 60° C. The mixture was stirred at 60° C. for 1 h. The reaction was concentrated and purified by a silica gel column (eluting with 3% $\text{Et}_3\text{N}/\text{THF}$) to give 44 (5.2 g, yield 56.5%). ^1H NMR (300 MHz, CDCl_3) δ : 3.2-3.1 (s, 2H) 2.9-2.9 (m, 3H), 2.6-2.5 (m, 2H), 1.6-1.5 (s, 2H), 1.4-1.3 (s, 11H).

To a solution of 44 (3.2 g, 14.8 mmol) was added 8-oxaspiro[4.5]decane-7,9-dione (2.9 g, 17.7 mmol) in DCM (30 mL). The resulting mixture was stirred at RT for 1 h. Then, the mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4 , and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 45 (3.5 g, yield 62.5%). ^1H NMR (300 MHz, CDCl_3) δ : 3.5-3.4 (m, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.5 (m, 4H), 1.8-1.4 (s, 25H).

To a solution of 45 (3.5 g, 9.1 mmol) in 40 mL DCM was added $\text{Et}_2\text{O}/\text{HCl}$ slowly (4 mol/L, 40 mL) under ice bath. Then, the mixture was stirred at room temperature overnight. The mixture was concentrated and washed with Et_2O to give 46 (2.2 g, yield 75.8%). ^1H NMR (300 MHz, DMSO) δ : 3.5-3.4 (m, 2H), 3.3 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.5 (m, 4H), 1.8-1.4 (s, 16H).

To a solution of 46 (2.2 g, 6.8 mmol) and potassium carbonate (1.9 g, 13.7 mmol) in acetonitrile (20 mL) and water

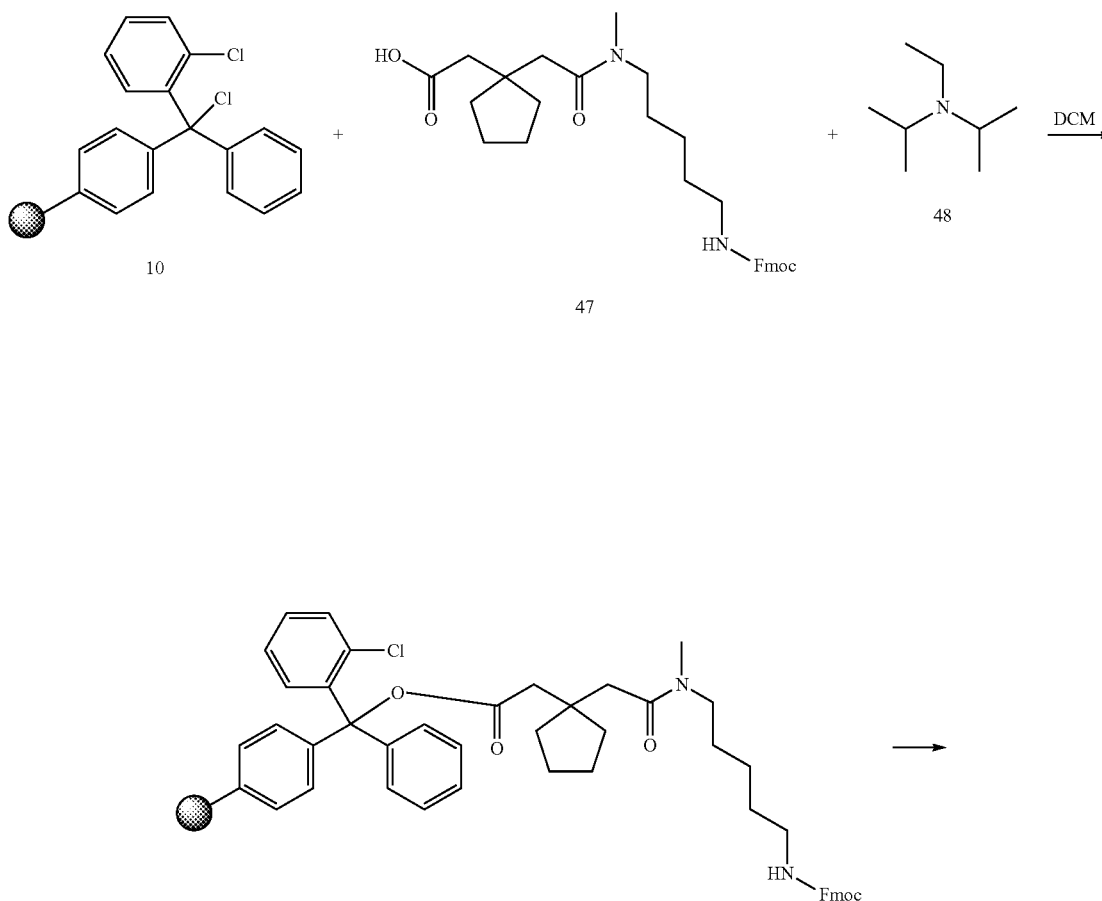
80

(40 mL) was added Fmoc-osu (2.5 g, 7.5 mmol) in acetonitrile (20 mL) over 10 minutes under an ice bath. The mixture was stirred under ice bath for about 1 h. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na_2SO_4 , and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 47 (2 g, yield 58.8%). ^1H NMR (300 MHz, CDCl_3) δ : 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.6-7.5 (d, 2H), 7.4-7.3 (m, 2H), 7.3-7.2 (d, 2H), 4.5-4.4 (m, 2H), 4.2 (m, 1H), 3.5-3.4 (m, 2H), 3.2 (m, 2H), 3.1 (m, 2H), 3.0 (m, 1H), 2.6-2.5 (m, 4H), 1.8-1.4 (s, 12H), 1.4-1.2 (s, 2H). LC-MS: m/z =529.2 ($\text{M}+23$) $^+$.

The resulting product 47 was employed as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compound 421. Alternatively, the resulting product was employed as intermediate 11 in Scheme 1 to produce compounds wherein R^1 is $-\text{N}(\text{CH}_3)-$ and R^2 is $-(\text{CH}_2)_5-\text{N}(\text{H})-\text{C}(\text{O})-\text{C}(\text{H})(\text{R}^{11})-(\text{CH}_2)_{0-2}-$. For other compounds of the invention, the resulting product was used as set forth in Example 9, below.

Example 9

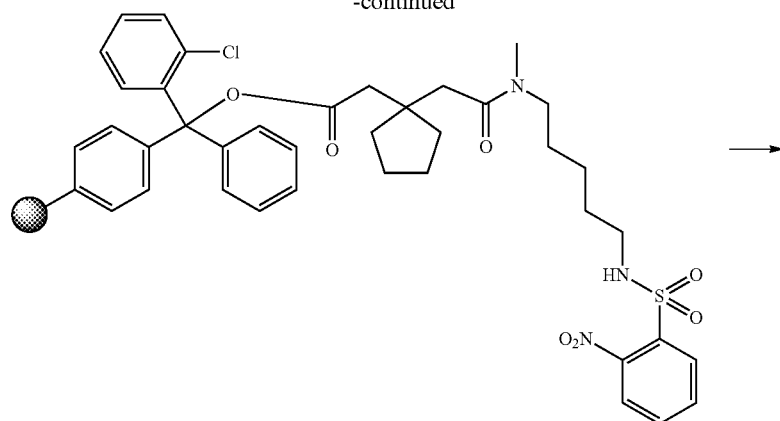
Synthesis of Resin-Linked Intermediate 51



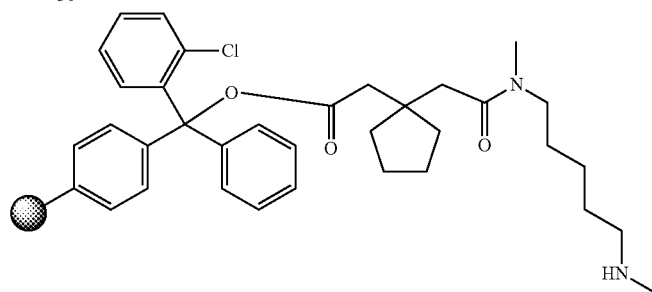
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2-Chlorotrityl chloride resin (10; 0.658 g, 0.790 mmol) was added to a 20 mL plastic column. The resin was swelled with 10 mL anhydrous DCM and let sit for 20 minutes. The DCM was drained and the resin washed with 10 mL of DCM. 2-(1-(2-(((9H-Fluoren-9-yl)methoxy)carbonylamino)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic acid (47; 0.400 g, 0.790 mmol) and N-ethyl-N-isopropylpropan-2-amine (48; 0.688 mL, 3.95 mmol) were dissolved in DCM (30 mL) in a 10 mL vial. The solution was loaded onto column containing the resin and rocked overnight. The solution was drained from the column, which was then washed with 85:10:5 DCM:MeOH:DIPEA (10 mL \times 2) and DCM (10 mL \times 3), and dried under light vacuum to produce resin 49. Resin loading was measured to be 0.3 mmol/g.

850 mg of resin 49 from the previous step was swelled in DMF (8 mL) for 15 min. The DMF was drained and 8 mL of 2% piperidine/2% DBU in DMF was added. After rotation for 5 min, the solution was drained and the resin washed 1 \times with DMF. 8 mL of 2% piperidine/2% DMF in DMF was added to the resin and rotated for 15 min. The solution was drained and the resin washed 5 \times with DMF. In a separate vial, 2-nitrobenzenesulfonyl chloride (0.222 g, 1.000 mmol) was dissolved in DMF (8 mL). To that was added 2,4,6-Collidine (0.330 mL, 2.500 mmol) and the mixture was vortexed. The NBS/collidine solution was added to the resin and rotated for 15 min.

After draining the resin was washed 1 \times with DMF, and the treatment with NBS/collidine was repeated. The resulting resin 50 was washed 5 \times with DMF.

The resin 50 from the previous step was rinsed 2 \times with THF. In a vial, triphenylphosphine (0.328 g, 1.250 mmol) was dissolved in DMF (5 mL), MeOH (0.101 mL, 2.500 mmol) added, and the solution mixed well. The solution was added to the resin and rotated vigorously for 2 min. Diisopropyl azodicarboxylate (0.246 mL, 1.250 mmol) dissolved in THF (1 mL) was added to the resin in 200 μ L portions and rocked for 10 min between each addition. The resin was then rocked overnight. The solution was drained from resin and resin was washed with THF (5 \times 5 mL) followed by DCM (3 \times 5 mL). The additions of triphenylphosphine and diisopropyl azodicarboxylate were repeated and the resin rocked for an additional 8 hours. In a separate vial, 2-mercaptoethanol (0.176 mL, 2.500 mmol) was dissolved in DMF (5 mL) and then DBU (0.188 mL, 1.250 mmol) was added. This solution was added to the resin and rotated for 5 min. The reaction solution was drained from the resin and the resin washed with DMF (2 \times 5 mL). The resulting resin 51 was then washed thoroughly with DMF, followed by DCM.

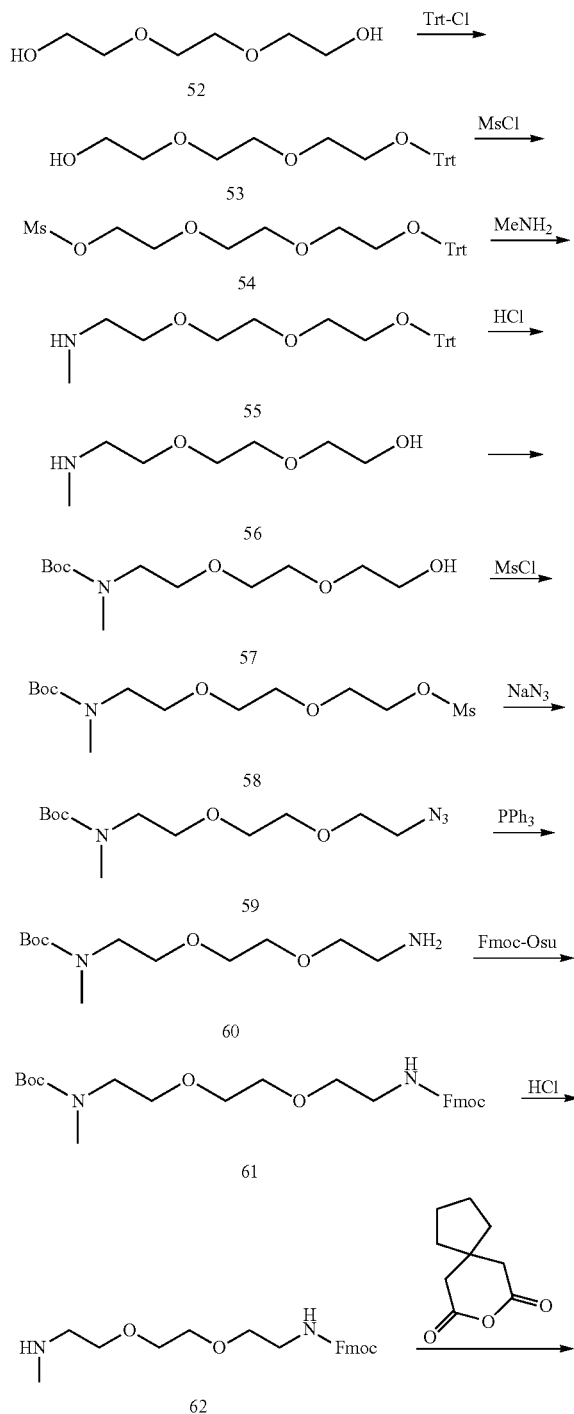
For certain compounds of the invention, the resulting resin 51 was used as resin 12 in general Scheme 1. For other compounds of the invention, the resulting resin 51 was used as resin 16 in general Scheme 2, e.g., Compounds 387, 488,

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489, 524, 525, 566, 570, 600, 601, 602, 623, 625, 626, 627, 628, 629, 630, 631, 644, 645, 646, 653, 665, 669, and 670.

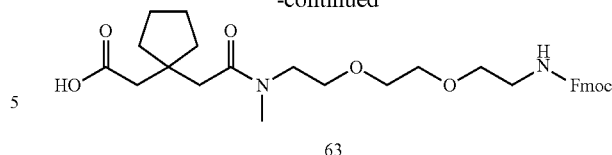
Example 10

Synthesis of 2-(1-(9H-fluoren-9-yl)-13-methyl-3,14-dioxo-2,7,10-trioxa-4,13-diazapentadecan-15-yl)cyclopentyl)acetic Acid (63)



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To a solution of 2,2'-(ethane-1,2-diylbis(oxy))diethanol (52; 100 g, 667 mmol) and Et₃N (18.5 mL, 133 mmol) in DCM (500 mL) was added triphenylmethyl chloride (abbreviated as (Trt-Cl) (18.6 g, 66.7 mmol) in DCM (10 mL) over 20 minutes under an ice bath. The progress of the reaction was checked by TLC. The solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 5-15% EA/PE, 1% Et₃N) to provide 53 (15 g, yield: 57.3%). ¹H NMR (300 MHz, CDCl₃) δ: 7.6-7.4 (m, 5H), 7.4-7.2 (m, 10H), 3.8-3.6 (m, 6H), 3.6-3.5 (m, 2H), 3.3-3.1 (m, 2H), 2.5-2.3 (s, 1H).

To a solution of 53 (15 g, 38.2 mmol) in DCM (100 mL) and Et₃N (8 mL, 45.9 mmol) was added methanesulfonyl chloride (5.2 g, 45.9 mmol) in portions over 10 minutes under an ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give 54 (17 g, yield: 94.7%). ¹H NMR (300 MHz, CDCl₃) δ: 7.6-7.4 (m, 5H), 7.4-7.2 (m, 10H), 4.5-4.3 (m, 2H), 3.9-3.8 (m, 2H), 3.8-3.6 (m, 6H), 3.0 (s, 3H).

To a solution of 54 (17 g, 36 mmol) in THF (20 mL) was added CH₃NH₂ aqueous solution slowly (30%, 80 mL) at 60° C. The mixture was stirred at 60° C. for 4 h. The mixture was concentrated to provide 55 (14.5 g, yield: 99.8%). ¹H NMR (300 MHz, CDCl₃) δ: 7.7-7.4 (m, 7H), 7.4-7.2 (m, 8H), 3.9-3.7 (m, 8H), 3.3-3.2 (m, 2H), 2.8-2.8 (m, 2H), 2.5-2.4 (s, 3H).

To a solution of 55 (4.5 g, 36.1 mmol) in 30 mL DCM was added Et₂O/HCl (5.2 mol/L, 50 mL) at room temperature. Then, the mixture was stirred at room temperature over night. The mixture was filtered and the residue was washed with Et₂O to give 56 (7.2 g, yield: 99.6%).

To a solution of 56 (7.2 g, 36.1 mmol) in DCM (0.2 L) was added (Boc)₂O dropwise (42.3 g, 194 mmol) under ice bath. The reaction was stirred at RT overnight. Then the mixture solution was extracted with DCM and washed with water. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum and purified by a silica gel column (eluting with 20-50% EA/PE) to provide 57 (7 g, yield: 73.7%). ¹H NMR (300 MHz, CDCl₃) δ: 3.8-3.6 (m, 11H), 3.5-3.3 (m, 2H), 3-2.8 (s, 3H), 1.6-1.5 (s, 9H).

To a solution of 57 (7 g, 26.6 mmol) in DCM (100 mL) and Et₃N (5.5 mL, 40 mmol) was added methanesulfonyl chloride (3.6 g, 32 mmol) in portions over 10 minutes under ice bath. The reaction was stirred for 1 hour. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated to give 58 (8 g, yield: 89.4%). ¹H NMR (300 MHz, CDCl₃) δ: 4.5-4.3 (m, 2H), 3.9-3.7 (m, 2H), 3.7-3.5 (m, 6H), 3.5-3.3 (s, 2H), 3.1 (s, 3H), 3-2.8 (s, 3H), 1.6-1.5 (s, 9H).

To a solution of 58 (8 g, 30.4 mmol) in DMF (0.1 L) was added sodium azide (3.2 g, 49.7 mmol) under an ice bath. The reaction was stirred ice bath for 4 h, H₂O (5 mL) was added

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and the mixture was stirred at room temperature for overnight. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum to provide 59 (7 g, yield: 79.9%). ¹H NMR (300 MHz, CDCl₃) δ: 3.8-3.5 (m, 6H), 3.5-3.4 (m, 2H), 3.1-2.8 (m, 5H), 1.6-1.5 (s, 9H).

To a solution of 59 (7.0 g, 24.3 mmol) in THF (50 mL) was added PPh₃ (7.6 g, 29.1 mmol) under an ice bath. The reaction was stirred ice bath for 4 h, H₂O (5 mL) was added and the mixture was stirred at room temperature for overnight. Then, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum to provide 60 (5.6 g, yield: 62.3%).

To a solution of 60 (5.6 g, 21.4 mmol) and potassium carbonate (4.4 g, 32 mmol) in acetonitrile (25 mL) and water (25 mL) was added Fmoc-Osu (7.9 g, 23.5 mmol) in acetonitrile (25 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50/90% EA, 10% MeOH) to provide 61 (9.5 g, yield: 91.7%). ¹H NMR (300 MHz, CDCl₃) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.3 (m, 4H), 4.6-4.4 (m, 2H), 4.4-4.3 (m, 1H), 3.8-3.5 (m, 7H), 3.5-3.2 (m, 4H), 3.0-2.8 (s, 3H), 1.6-1.5 (s, 9H).

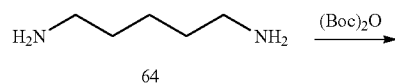
To a solution of 61 (9.5 g, 19.6 mmol) in 30 mL DCM was added Et₂O/HCl (5.2 mol/L, 40 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. The mixture was filtered and the residue was washed with Et₂O to give of 62 (8.6 g, yield: 99.6%).

To a solution of 62 (8.6 g, 19.5 mmol) and DIEA (3.3 g, 25.2 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (4.2 g, 25.2 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. The solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to provide 63 (10 g, yield: 92.9%). ¹H NMR (300 MHz, CDCl₃) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.4 (m, 2H), 4.3-4.1 (m, 1H), 3.7-3.5 (m, 9H), 3.5-3.3 (m, 2H), 3.2-3.1 (m, 2H), 3.0-2.9 (m, 1H), 2.7-2.4 (m, 4H), 1.8-1.6 (m, 6H), 1.6-1.4 (m, 2H). LC-MS: m/z=575 (M+23)⁺.

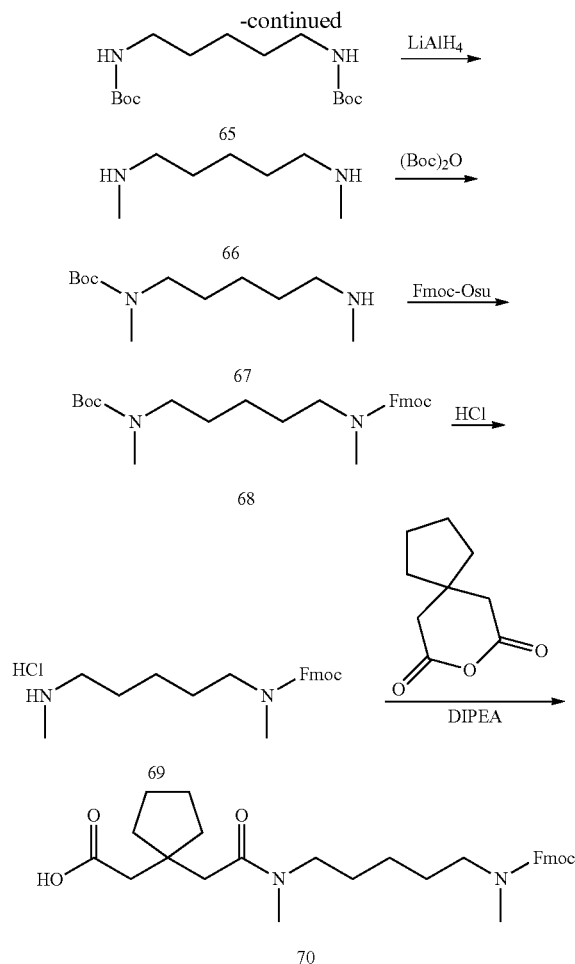
The resulting product 63 is used as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compounds 565, 568, 581, 582, and 585.

Example 11

Alternate Synthesis of 2-(1-(2-(((5-(((9H-fluoren-9-yl)methoxy)carbonyl)(methyl)amino)pentyl)(methyl)amino)-2-oxoethyl)cyclopentyl)acetic Acid (70)



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To a solution of pentane-1,5-diamine (64; 10 g, 98 mmol) and potassium carbonate (27 g, 196 mmol) in 1,4-dioxane (50 mL) and H₂O (50 mL) was added (Boc)₂O (42.8 g, 196 mmol) in 1,4-dioxane (50 mL) over 10 minutes under an ice bath. The reaction was stirred at room temperature for overnight. Then, the mixture solution was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The solvent was removed in vacuum to give 65 (26.1 g, yield 88.2%). ¹H NMR (300 MHz, CDCl₃) δ: 4.7-4.5 (m, 2H), 3.2-3.0 (m, 6H), 1.8-1.7 (m, 2H), 1.6-1.4 (s, 18H), 1.4-1.3 (m, 2H).

To a solution of 65 (26.1 g, 86 mmol) in THF (200 mL) was added LiAlH₄ (13 g, 344 mmol) over 20 minutes under an ice bath. The reaction was refluxed for 16 h. After the reaction mixture was cooled, saturated NaOH (10 mL) was added. The mixture was filtered and the residue was washed with THF. Then, the filtrate was concentrated under vacuum to give 66 without purification (7 g, yield: 61.9%). ¹H NMR (300 MHz, CDCl₃) δ: 4.7-4.5 (m, 2H), 3.2-3.0 (m, 6H), 2.9-2.8 (m, 6H), 1.7-1.6 (m, 2H), 1.3-1.2 (m, 2H).

To a solution of 66 (7 g, 53.4 mmol) and potassium carbonate (14.7 g, 106.8 mmol) in 1,4-dioxane (30 mL) and H₂O (30 mL) was added (Boc)₂O (11.6 g, 53.4 mmol) in 1,4-dioxane (30 mL) over 20 minutes under ice bath. The mixture was stirred at room temperature overnight. The reaction was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50% EA/PE, 5% MeOH) to give 67 (6.2 g, yield: 50%).

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To a solution of 67 (6.2 g, 26.9 mmol) and potassium carbonate (3.7 g, 26.9 mmol) in acetonitrile (25 mL) and water (25 mL) was added Fmoc-Osu (8.1 g, 24.3 mmol) in acetonitrile (25 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE) to provide 68 (9.8 g, yield: 89.3%). ¹H NMR (300 MHz, CDCl₃) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.2 (m, 3H), 3.4-3.0 (m, 4H), 2.9-2.8 (m, 6H), 1.6-1.5 (s, 9H), 1.4-1.0 (m, 6H), 1.0-0.8 (m, 4H).

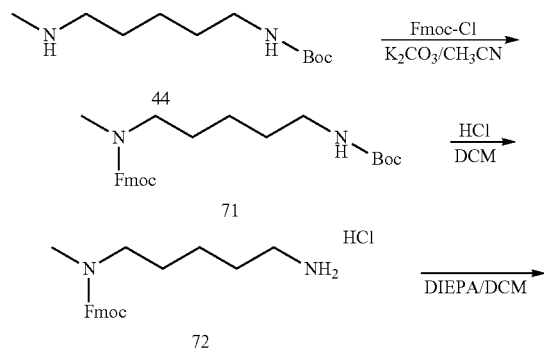
To a solution of 68 (9.8 g, 21.7 mmol) in 20 mL DCM was added Et₂O/HCl (5.2 mol/L, 20 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. The mixture was filtered and the residue was washed with Et₂O to give 69 as a white solid (8.2 g, yield 97.6%). ¹H NMR (300 MHz, D₂O) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.3 (m, 4H), 4.6-4.4 (m, 2H), 4.3-4.2 (m, 1H), 3.4-3.2 (m, 1H), 3.2-3.0 (m, 1H), 2.9-2.8 (m, 3H), 1.7-1.6 (m, 2H), 1.6-1.2 (m, 3H), 1.0-0.8 (m, 3H).

To a solution of 69 (8.6 g, 22.1 mmol) and DIEA (8.5 g, 66.3 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (3.7 g, 22.1 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. Next, the solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to provide 70 (10 g, yield: 86.9%). ¹H NMR (300 MHz, CDCl₃) δ: 7.9-7.7 (d, 2H), 7.7-7.5 (m, 2H), 7.5-7.2 (m, 4H), 4.6-4.4 (m, 2H), 4.4-4.1 (m, 1H), 3.5-3.2 (m, 2H), 3.1-2.8 (m, 6H), 2.6-2.5 (m, 4H), 1.8-1.5 (m, 6H), 1.5-1.4 (m, 2H), 1.4-1.2 (m, 2H). LC-MS: m/z=520.4 (M+23)⁺.

The resulting product 70 is used as intermediate 15 in Scheme 2 to produce compounds of the invention such as Compounds 600, 601, 623, 625, 626, 627, 628, 629, 630, 631, 644, 645, 646, 653, 665, 669, and 670.

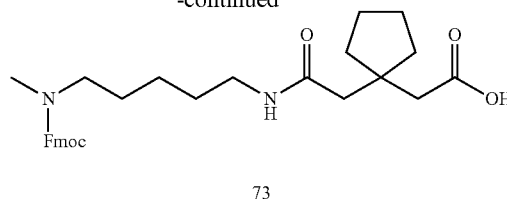
Example 12

Synthesis of 2-(1-(2-(5-(((9H-fluoren-9-yl)methoxy)carbonyl)pentylamino)-2-oxoethyl)cyclopentyl)acetic Acid (73)



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-continued



To a solution of 44 (from Example 8; 3.2 g, 14.8 mmol) and potassium carbonate (4.1 g, 29.6 mmol) in acetonitrile (20 mL) and water (40 mL) was added Fmoc-Cl (4.2 g, 16.3 mmol) in acetonitrile (20 mL) over 10 minutes under an ice bath. The mixture was stirred under an ice bath for about 2 h. The mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE) to give 71 (4.3 g, yield: 66.2%). ¹H NMR (300 MHz, CDCl₃) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.4 (d, 2H), 7.4-7.3 (m, 2H), 4.5-4.4 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.4 (s, 11H).

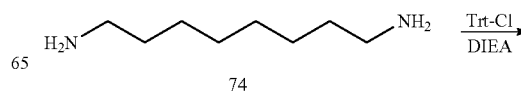
To a solution of 71 (4.3 g, 9.8 mmol) in 40 mL DCM was added Et₂O/HCl slowly (4 mol/L, 40 mL) under ice bath. Then, the mixture was stirred at RT overnight. The mixture was concentrated and washed with Et₂O to give 72 (3 g, yield 83.4%). ¹H NMR (300 MHz, CDCl₃) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.4 (d, 2H), 7.4-7.3 (m, 2H), 4.5 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.4 (s, 2H).

To a solution of 72 (3 g, 8.0 mmol) and DIEA (2 g, 16.0 mmol) in DCM (20 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (1.5 g, 8.8 mmol). The mixture was stirred at RT for 1 h. The mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-30% EA/PE, 2% AcOH) to give 73 (3.1 g, yield 77.5%). ¹H NMR (300 MHz, CDCl₃) δ: 7.9-7.8 (d, 2H), 7.7-7.6 (d, 2H), 7.6-7.5 (d, 2H), 7.4-7.3 (m, 2H), 7.3-7.2 (d, 2H), 4.5 (m, 1H), 4.4 (m, 1H), 4.3 (m, 1H), 3.3-3.2 (m, 3H), 2.9-2.8 (m, 3H), 2.4 (m, 2H), 2.2 (m, 1H), 1.8-1.5 (s, 9H), 1.5-1.3 (s, 5H). LC-MS: m/z=529.2 (M+23)⁺.

The resulting product 73 is used as intermediate 15 in Scheme 2 to produce compounds of the invention such as Compound 422. Alternatively, 73 was used as intermediate 11 in general Scheme 11 to produce compounds of the invention, such as Compounds 281, 307, 308, 335, 351, 363, 470 and 518.

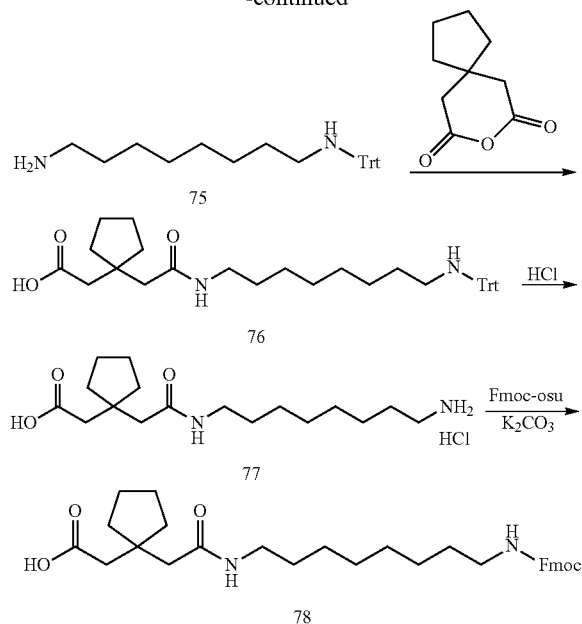
Example 13

Synthesis of 2-(1-(2-(8-(((9H-fluoren-9-yl)methoxy)carbonyl)octylamino)-2-oxoethyl)cyclopentyl)acetic Acid (78)



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-continued



To a solution of 74 (10 g, 69.5 mmol) and DIEA (8.9 g, 69.5 mmol) in DCM (100 mL) was added triphenylmethyl chloride (abbreviated as Trt-Cl) (9.66 g, 34.75 mmol) in DCM (20 mL) over 10 minutes under an ice bath. The mixture was stirred overnight at room temperature. After TLC, the mixture was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 50% EA/PE-10% MeOH) to give 75 (8.8 g, yield 65.7%).

To a solution of 75 (8.8 g, 22.7 mmol) and DIEA (2.94 g, 22.7 mmol) in DCM (50 mL) was added 8-oxaspiro[4.5]decane-7,9-dione (3.82 g, 22.7 mmol) in DCM (10 mL) over 5 minutes under an ice bath. The progress of the reaction was checked by TLC. Next, the solution was extracted with DCM. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE, 2% AcOH) to give 76 (8.6 g, yield 68.3%).

To a solution of 76 (8.6 g, 15.5 mmol) in 20 mL DCM was added Et₂O/HCl (5.2 mol/L, 10 mL) at room temperature. Then, the mixture was stirred at room temperature overnight. Next, the mixture was filtered and the residue was washed with Et₂O to give 77 as a white solid (4.6 g, yield 85%).

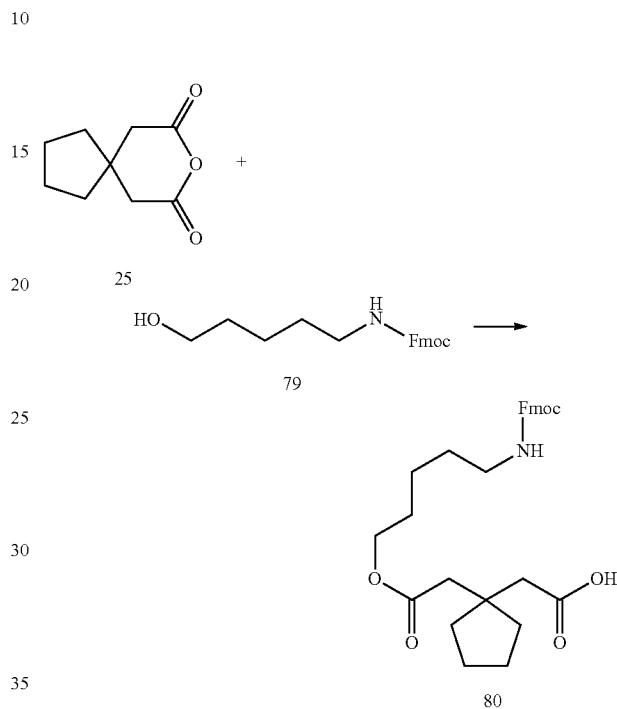
To a solution of 77 (4.6 g, 13.2 mmol) and potassium carbonate (3.6 g, 26.3 mmol) in acetonitrile (30 mL) and water (30 mL) was added Fmoc-Osu (4.44 g, 13.2 mmol) in acetonitrile (20 mL) over 10 minutes under ice bath. The mixture was stirred for 30 minutes. After TLC, the mixture was extracted with EA. The combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, and filtered. The filtrate was concentrated and purified by a silica gel column (eluting with 20-50% EA/PE) to give 78 (5.8 g, yield 82.3%). ¹H NMR (300 MHz, CDCl₃) δ: 7.8-7.7 (d, 2H), 7.7-7.6 (d, 2H), 7.5-7.3 (m, 4H), 4.5-4.4 (m, 2H), 4.4-4.3 (m, 2H), 3.3-3.1 (m, 4H), 2.5-2.4 (s, 2H), 2.4-2.3 (s, 2H), 1.8-1.7 (m, 4H), 1.7-1.6 (m, 2H), 1.6-1.4 (m, 6H), 1.4-1.3 (m, 9H). LC-MS: m/z=557.4 (M+23)⁺.

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The resulting product 78 is used as intermediate 15 in Scheme 2 to produce compounds of the invention, such as Compounds 337, 366, 441, 442, 505, 597, 598, and 599.

Example 14

Synthesis of 2-(1-(2-((5-(((9H-fluoren-9-yl)methoxy)carbonyl)amino)pentyl)oxy)-2-oxoethyl)cyclopentyl)acetic Acid



A 250-mL round bottom flask, equipped with magnetic stirring bar, is charged with 8-oxaspiro[4.5]decane-7,9-dione (25; 1.2 g, 7.1 mmol), (9H-fluoren-9-yl)methyl(5-hydroxypentyl)carbamate (79; 2.3 g, 7.1 mmol), N,N-dimethylpyridin-4-amine (0.9 g, 7.4 mmol), and dichloromethane (125 mL). The resulting mixture is stirred at room temperature for overnight. Next, the solvent was removed by rotary evaporation. The crude product is purified by silica gel chromatography (40 g, dichloromethane/acetonitrile: 100:0 to 50:50 ratio.) to obtain desired product 80 (1.67 g, 47.7%).

The resulting product 80 was then used as intermediate 11 in general Scheme 1 to produce compounds of the invention wherein —R¹-R²— is —O—(CH₂)₅—NH—C(O)—C(H)(R¹¹)—(CH₂)₀₋₂—, such as Compounds 671, 672, 673, 674, 675, 676, 677, 678, 679, 680 and 681.

Mass Spectrometry values for exemplary compounds of the invention are set forth in Table 2. NMR data for select compounds are set forth after Table 2.

TABLE 2

Physical data for Exemplary Compounds of the Invention.

Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
100	756.38	756.33
101	841.43	841.34
102	742.36	742.21
103	827.42	827.3

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.			5
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)	
104	823.44	823.38	10
105	841.42	841.34	
106	841.42	841.34	
107	841.42	841.34	
108	813.39	813.32	
109	827.41	827.37	15
110	855.44	855.39	
111	869.46	869.36	
112	857.39	857.31	
113	843.37	843.26	
114	823.44	823.3	20
115	809.43	809.33	
116	841.43	841.34	
117	827.42	827.3	
118	841.25	841.34	
119	827.42	827.3	25
120	901.35	901.29	
121	887.34	887.25	
122	789.46	789.37	
123	775.44	775.33	
124	899.47	899.44	30
125	885.46	885.4	
126	837.46	837.35	
127	823.44	823.38	
128	827.42	827.37	
129	756.38	756.33	35
130	742.36	742.28	
131	742.36	742.28	
132	875.42	875.34	
133	861.40	861.37	
134	861.40	861.37	40
135	875.42	875.34	
136	827.42	827.3	
137	827.42	827.37	
138	823.44	823.38	
139	809.43	809.33	45
140	891.43	891.31	
141	829.37	829.22	
142	815.36	815.25	
143	829.37	829.22	
144	815.36	815.25	50
145	857.40	857.31	
146	843.39	843.26	
147	859.38	859.23	
148	845.37	845.26	
149	813.40	813.25	55
150	799.39	799.28	
151	799.39	799.28	
152	667.30	667.18	
153	695.33	695.20	
154	709.35	709.17	60
155	723.37	723.21	
156	743.33	743.17	
157	757.35	757.22	
158	771.37	771.19	
159	771.37	771.34	65
160	785.38	785.23	
161	799.40	799.20	
162	757.35	757.14	
163	681.32	681.15	
164	771.37	771.19	60
165	695.33	695.2	
166	785.38	785.23	
167	709.35	709.17	
168	815.39	815.25	
169	739.36	739.18	65
170	829.41	829.22	
171	753.38	753.22	
172	843.42	843.26	
173	767.39	767.27	
174	827.42	827.22	65
175	827.42	827.22	
176	827.42	827.22	
177	799.39	799.20	

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
178	871.44	871.28
179	742.36	742.21
180	815.36	815.17
181	815.36	815.25
182	843.39	843.26
183	753.40	753.22
184	773.39	773.18
185	805.33	805.35
186	729.44	729.97
187	815.32	815.71
188	785.38	785.75
189	769.39	769.77
190	789.38	789.96
191	821.32	821.92
192	745.43	745.95
193	801.38	801.95
194	758.34	758.83
195	758.34	758.83
196	748.31	748.84
197	771.34	771.84
198	775.33	775.91
199	772.35	772.95
200	759.33	759.86
201	759.33	759.86
202	772.35	772.95
203	775.33	775.91
204	791.30	791.89
205	791.30	791.89
206	737.37	737.35
207	763.39	763.37
208	758.34	758.9
209	773.35	773.92
210	807.31	807.72
211	831.31	831.91
212	772.35	772.95
213	772.35	772.95
214	773.34	773.84
215	773.34	773.84
216	787.35	787.89
217	787.35	787.89
218	801.37	801.95
219	787.35	787.31
220	765.37	765.92
221	717.32	717.38
222	745.35	745.4
223	785.38	785.39
224	806.31	806.31
225	822.26	822.27
226	772.35	772.3
227	775.33	775.4
228	743.36	743.40
229	743.36	743.40
230	727.38	727.43
231	703.42	703.48
232	744.36	744.36
233	793.38	793.37
234	725.34	725.36
235	748.31	748.35
236	777.40	777.33
237	737.40	737.34
238	751.42	751.38
239	771.37	771.34
240	771.37	771.34
241	805.33	805.27
242	772.35	772.30
243	711.37	711.32
244	701.40	701.19
245	675.39	675.39
246	715.42	715.38
247	689.40	689.36
248	753.34	753.16
249	845.37	845.34
250	816.35	816.29
251	703.42	703.41

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.			
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)	
252	627.39	627.42	
253	719.42	719.45	
254	690.40	690.4	
255	717.35	717.38	
256	641.31	641.39	10
257	733.34	733.35	
258	704.33	704.37	
259	756.39	756.34	
260	802.37	802.32	
261	861.41	861.38	15
262	877.41	877.34	
263	772.39	772.38	
264	739.32	739.26	
265	831.35	831.29	
266	802.34	802.24	
267	834.47	834.39	20
268	825.47	825.37	
269	901.46	901.29	
270	731.30	731.28	
271	793.32	793.30	
272	807.33	807.30	
273	710.34	710.28	
274	724.36	724.26	25
275	779.39	779.33	
276	793.42	793.30	
277	791.33	791.22	
278	791.33	791.29	
279	787.36	787.16	
280	785.38	785.31	30
281	785.38	785.31	
282	787.44	787.38	
283	754.37	754.38	
284	856.38	856.28	
285	829.37	829.30	
286	785.38	785.31	35
288	785.38	785.31	
289	799.40	799.29	
290	785.38	785.31	
291	799.40	799.36	
292	760.35	760.30	
293	743.45	743.40	
294	759.45	759.22	40
295	747.43	747.24	
296	807.34	807.27	
297	793.33	793.30	
298	807.34	807.27	
299	801.34	801.28	
300	778.41	778.29	45
301	764.39	764.32	
302	786.37	786.48	
303	738.37	738.30	
304	780.39	780.29	
305	789.36	789.23	
306	789.36	789.23	50
307	801.38	801.28	
308	789.36	789.31	
309	865.39	865.30	
310	703.42	703.33	
311	703.42	703.33	
312	703.42	703.33	55
313	689.40	689.36	
314	689.40	689.36	
315	729.44	729.36	
316	773.42	773.34	
317	861.41	861.50	
318	772.35	772.40	60
319	801.38	801.40	
320	857.44	857.60	
321	815.39	815.40	
322	829.37	829.50	
323	786.37	786.40	
324	795.31	795.30	
325	825.34	825.23	65
326	811.32	811.26	

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
327	759.34	759.29
328	811.32	811.26
329	811.32	811.26
330	773.34	773.27
331	819.48	819.53
332	743.45	743.44
333	718.42	718.45
334	714.46	714.45
335	743.45	743.40
336	849.49	849.60
337	744.47	744.40
338	772.36	772.43
339	815.35	815.39
340	801.37	801.38
341	842.40	842.45
342	743.45	743.59
343	773.46	773.61
344	748.43	748.54
345	728.36	728.28
346	686.43	686.50
347	742.37	742.41
348	700.44	700.55
349	770.37	770.50
350	728.48	728.58
351	773.46	773.54
352	774.42	774.50
353	772.36	772.43
354	758.37	758.45
355	716.44	716.51
356	772.38	772.50
357	730.46	730.57
358	800.42	800.53
359	758.49	758.60
360	773.46	773.54
361	730.43	730.47
362	716.42	716.45
363	841.44	841.55
364	770.37	770.43
365	784.38	784.48
366	742.37	742.48
367	829.37	829.42
368	816.35	816.41
369	787.44	787.47
370	774.42	774.43
371	806.46	806.51
372	812.45	812.50
373	765.42	765.55
374	765.42	765.55
375	759.44	759.56
376	731.41	731.39
377	653.40	653.38
378	745.43	745.36
379	715.42	715.37
380	747.62	747.41
381	730.43	730.43
382	733.41	733.38
383	805.47	805.48
384	760.41	760.45
385	865.34	865.45
386	789.36	789.44
387	799.40	799.49
388	807.35	807.47
390	785.38	785.51
391	700.33	700.48
392	714.34	714.53
393	730.34	730.50
394	744.35	744.48
395	735.45	735.48
396	749.38	749.51
397	716.32	716.38
398	686.31	686.36
399	729.35	729.42
400	746.33	746.40
401	716.32	716.53

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
402	759.36	759.49
403	733.41	733.53
404	783.41	783.52
405	933.44	933.62
406	747.33	747.30
407	715.46	715.50
408	819.37	819.38
409	645.38	645.39
410	676.39	676.58
411	715.34	715.27
412	745.35	745.29
413	785.38	785.44
414	815.39	815.46
415	723.39	723.55
416	890.44	890.59
417	705.40	705.40
418	740.36	740.39
420	687.31	687.28
421	673.41	673.41
422	673.41	673.41
423	660.34	660.40
424	736.41	736.40
425	871.43	871.50
425	871.43	871.83
426	891.42	891.47
427	829.39	829.51
428	822.37	822.49
429	822.37	822.49
430	982.58	982.71
431	948.48	948.62
432	842.44	842.52
433	876.42	876.54
434	821.36	821.52
435	880.40	880.42
436	807.46	807.44
437	906.55	906.63
438	1024.51	1024.56
439	990.49	990.55
440	827.28	827.37
441	772.39	772.43
442	743.37	743.39
443	786.37	786.48
444	863.39	863.52
445	877.41	877.50
446	770.35	770.43
447	772.36	772.44
448	699.42	699.46
449	766.43	766.51
450	766.43	766.51
451	832.35	832.39
452	771.37	771.39
453	776.34	776.40
454	815.36	815.46
455	875.38	875.49
456	682.30	682.29
457	801.38	801.41
458	697.41	697.52
459	844.38	844.52
460	776.32	776.60
461	774.33	774.60
462	857.44	857.92
463	775.36	775.66
464	699.33	699.59
465	700.31	700.40
466	731.33	731.62
467	745.35	745.61
468	709.35	709.73
469	817.39	817.80
470	817.39	817.80
471	871.43	871.98
472	887.39	887.96
473	873.40	873.90
474	803.37	803.84
475	796.33	796.81

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TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
476	783.43	783.86
477	792.36	792.82
478	758.40	758.86
479	860.39	860.90
480	831.40	831.90
481	728.37	728.70
482	845.38	845.44
483	801.38	801.44
484	776.34	776.41
485	744.37	744.44
486	817.39	817.48
487	815.39	815.50
488	831.40	831.47
489	845.42	845.42
490	778.34	778.45
491	810.38	810.47
492	803.37	803.45
493	851.37	851.43
494	774.37	774.46
495	774.37	774.46
496	774.37	774.46
497	756.33	756.40
498	796.37	796.50
499	885.45	885.50
500	759.33	759.40
501	799.37	799.50
502	796.33	796.40
503	743.37	743.50
504	818.37	818.53
505	814.41	814.54
506	899.46	899.64
507	877.43	877.54
508	838.38	838.57
509	837.47	837.61
510	798.42	798.57
511	823.46	823.63
512	815.43	815.57
513	873.38	873.47
514	929.44	929.51
515	840.45	840.56
516	731.38	731.60
518	831.40	831.54
519	771.36	771.58
520	849.37	849.59
521	764.32	764.46
522	746.33	746.44
523	769.39	769.54
523	769.39	769.58
523	769.39	769.51
524	908.43	908.70
525	817.39	817.60
526	771.36	771.60
527	930.40	930.55
528	904.38	904.54
529	847.36	847.51
530	814.32	814.46
531	820.38	820.51
532	802.39	802.51
533	848.37	848.54
534	830.38	830.43
535	789.35	789.47
536	807.34	807.45
537	762.33	762.41
538	780.32	780.45
539	846.41	846.63
540	864.40	864.67
541	830.38	830.45
542	848.37	848.51
543	803.37	803.60
544	776.34	776.53
545	776.34	776.53
546	730.34	730.54
547	730.34	730.54
548	774.33	774.53

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
549	799.36	799.60
550	801.37	801.60
551	801.37	801.60
552	828.42	828.66
553	803.39	803.60
554	775.34	775.50
555	784.36	784.56
556	916.40	916.67
557	840.37	840.64
558	764.33	764.55
559	814.32	814.46
560	839.35	839.53
561	803.37	803.60
562	871.46	871.63
563	872.43	872.58
564	775.34	775.57
565	810.34	810.54
566	849.39	849.66
567	851.37	851.60
568	714.33	714.53
569	755.35	755.54
570	753.37	753.59
571	762.33	762.43
572	780.32	780.45
573	842.40	842.56
574	830.40	830.58
575	805.35	805.59
576	801.37	801.60
577	739.36	739.56
578	753.37	753.53
579	714.33	714.49
580	728.34	728.54
581	790.36	790.43
582	817.41	817.49
583	831.38	831.47
584	858.43	858.53
585	788.34	788.43
586	787.36	787.40
587	844.42	844.54
588	768.39	768.47
589	788.38	788.44
590	806.37	806.47
591	824.36	824.45
592	789.35	789.47
593	818.34	818.38
594	829.37	829.62
595	754.40	754.49
596	761.46	761.52
597	792.37	792.50
598	750.44	750.50
599	757.50	757.60
600	807.46	807.59
601	814.52	814.68
602	809.44	809.58
603	816.50	816.61
604	822.47	822.60
605	829.53	829.68
606	787.38	787.50
607	755.37	755.47
608	773.36	773.50
609	741.35	741.48
610	759.34	759.45
611	768.41	768.47
612	636.38	636.41
613	782.43	782.45
614	789.49	789.54
615	754.40	754.42
616	761.46	761.52
617	789.35	789.47
618	803.37	803.45
619	817.39	817.49
620	777.35	777.42
621	817.39	817.49
622	819.36	819.42

TABLE 2-continued

Physical data for Exemplary Compounds of the Invention.		
Cmpd No.	Exact Mass (M + H)	Observed Mass (M + H)
623	789.47	789.54
624	672.40	672.49
625	711.44	711.38
626	871.54	871.48
627	926.45	926.42
628	814.41	814.36
629	891.43	891.38
630	821.39	821.39
631	841.45	841.45
632	658.38	658.33
633	872.34	872.36
634	872.34	872.36
635	836.34	836.33
636	850.35	850.32
637	928.40	928.37
638	928.40	928.37
639	881.38	881.39
640	775.48	775.45
641	936.46	936.51
642	908.43	908.47
643	790.40	790.41
644	848.51	848.47
645	906.41	906.54
646	844.50	844.55
647	734.41	734.39
649	943.36	943.39
650	886.47	886.42
651	904.38	904.33
652	722.29	722.20
653	858.51	858.46
654	814.37	814.36
655	839.45	839.44
656	902.39	902.40
657	936.41	936.51
658	942.36	942.43
659	978.42	978.45
660	901.43	901.44
661	974.42	974.38
662	925.40	925.41
663	772.44	772.40
664	742.43	742.38
665	770.46	770.42
666	822.36	822.29
667	950.40	950.34
668	908.47	908.41
669	892.40	892.34
670	850.47	850.42
671	766.39	766.42
672	690.36	690.37
673	654.38	654.41
674	808.32	808.30
675	732.29	732.31
676	696.31	696.14
677	718.39	718.27
678	822.34	822.20
679	780.41	780.33
680	732.41	732.24
681	668.39	668.39

55 NMR Data.

Compound 159:

¹H NMR (300 MHz, DMSO-d₆) δ 9.96 (1H, s), 8.51 (3H, m), 8.01 (1H, t), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.12 (8H, m), 6.95 (1H, t), 4.76 (1H, q), 4.20 (1H, m), 3.76 (1H, dd), 3.50 (1H, dd), 3.44 (2H, d), 3.17-2.87 (7H, m), 2.76 (1H, m), 2.21 (2H, q), 2.12 (1H, d), 1.76 (1H, d), 1.65 (1H, m), 1.60-1.47 (3H, m), 1.45-1.29 (7H, m), 1.19 (3H, m), 0.86 (1H, m).

65 Compound 181:

¹H NMR (300 MHz, DMSO-d₆) δ 12.46 (1H, br), 9.98 (1H, s), 8.51 (3H, m), 8.23 (1H, d), 7.46 (2H, d), 7.37 (1H,

dd), 7.28 (1H, dd), 7.26-7.12 (9H), 7.06 (1H, t), 4.76 (1H, q), 4.19 (2H, m), 3.75 (1H, dd), 3.49 (1H, dd), 3.44 (2H, d), 3.18-2.93 (5H), 2.76 (1H, m), 2.21 (2H, d), 2.14 (1H, d), 1.85 (1H, d), 1.70-1.58 (3H), 1.58-1.47 (3H), 1.47-1.16 (7H), 0.91 (1H, m).

Compound 239:

¹H NMR (300 MHz, DMSO-d₆) δ 10.07 (1H, s), 8.54 (3H, m), 8.01 (1H, t), 7.45 (2H, d), 7.36 (1H, s), 7.26-7.15 (8H, m), 7.09 (2H, d), 6.95 (1H, t), 4.65 (1H, m), 4.20 (1H, m), 3.76 (1H, dd), 3.52-3.35 (4H, m), 3.30-2.70 (8H, m), 2.21 (2H, dd), 2.12 (1H, d), 1.77 (1H, d), 1.65 (1H, m), 1.60-1.30 (11H, m), 1.18 (2H, m), 0.86 (1H, m).

Compound 242:

¹H NMR (300 MHz, DMSO-d₆) δ 9.96 (1H, s), 8.48 (2H, m), 8.29 (1H, d), 7.43 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.10 (9H, m), 4.75 (1H, m), 4.27 (1H, m), 4.11 (1H, m), 3.79 (2H, m), 3.43 (2H, q), 3.35 (1H, d), 3.20-2.60 (8H, m), 2.28 (1H, d), 2.16 (1H, d), 2.12 (1H, s), 1.65-1.36 (12H, m), 1.25 (1H, m), 1.06 (1H, m).

Compound 244:

¹H NMR (300 MHz, DMSO-d₆) δ 9.97 (1H, s), 8.53 (2H, m), 8.34 (1H, d), 8.01 (1H, t), 7.87 (2H, d), 7.27 (3H, m), 7.20 (2H, d), 6.95 (1H, t), 4.46 (1H, q), 4.20 (1H, m), 3.76 (1H, dd), 3.49 (3H, m), 3.09 (2H, m), 2.95 (1H, dd), 2.88 (1H, m), 2.76 (1H, m), 2.21 (2H, q), 2.12 (1H, d), 1.76 (1H, d), 1.63 (2H, m), 1.57-1.30 (11H, m), 1.18 (2H, m), 0.86 (1H, m), 0.70 (1H, m), 0.32 (2H, m), 0.06 (2H, m).

Compound 256:

¹H NMR (300 MHz, DMSO-d₆) δ 12.50 (1H, br), 9.97 (1H, s), 9.23 (1H, br), 8.54 (2H, m), 8.37 (1H, d), 8.10 (1H, m), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.24-7.14 (4H, m), 7.06 (1H, t), 6.92 (2H, d), 6.60 (2H, d), 4.73 (1H, q), 4.22 (1H, m), 4.13 (1H, q), 3.75 (1H, dd), 3.48 (1H, dd), 3.17-2.93 (6H, m), 2.77 (1H, dd), 2.24 (2H, d), 2.12 (1H, d), 1.87 (1H, d), 1.69-1.16 (15H, m), 0.93 (1H, m).

Compound 181:

¹H NMR (300 MHz, DMSO-d₆) δ 12.46 (1H, br), 9.98 (1H, s), 8.51 (3H, m), 8.23 (1H, d), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.25-7.11 (8H, m), 7.06 (1H, t), 4.76 (1H, q), 4.19 (2H, m), 3.75 (1H, dd), 3.49 (1H, dd), 3.44 (1H, d), 3.18-2.93 (5H, m), 2.76 (1H, m), 2.24 (2H, d), 2.14 (1H, d), 1.85 (1H, d), 1.70-1.6 (3H, m), 1.58-1.47 (3H, m), 1.46-1.16 (7H, m), 0.91 (1H, m).

Compound 453:

¹H NMR (300 MHz, DMSO-d₆) δ 9.93 (1H, s), 9.24 (1H, s), 8.41 (2H, q), 8.23 (1H, q), 7.59 (1H, t), 7.41 (2H, d), 7.36 (1H, dd), 7.26 (1H, dd), 7.20 (1H, td), 7.15 (2H, m), 7.00 (1H, t), 6.61 (1H, m), 6.56 (2H, m), 4.74 (1H, q), 4.37 (1H, m), 3.53-3.33 (12H, m), 3.16-2.94 (5H, m), 2.71 (1H, q), 2.37 (1H, d), 2.23 (1H, d), 2.01 (1H, d), 1.69 (1H, d), 1.64-1.36 (5H, m), 1.09 (1H, m), 1.00 (1H, m), 0.77 (1H, m).

Compound 474:

¹H NMR (300 MHz, DMSO-d₆) δ 9.98 (1H, s), 8.49 (1H, d), 8.20 (1H, d), 7.99 (2H, m), 7.44 (2H, d), 7.37 (1H, d), 7.25 (2H, td), 7.18 (5H, m), 7.05 (2H, t), 7.56 (1H, m), 4.76 (1H, m), 4.21 (2H, m), 3.42 (4H, m), 3.27-2.83 (8H, m), 2.27 (2H, t), 2.05 (1H, d), 1.75 (2H, m), 1.52 (3H, m), 1.44-1.26 (6H, m), 1.22 (2H, d), 1.16 (2H, m), 0.83 (1H, m).

Compound 566:

¹H NMR (300 MHz, DMSO-d₆) δ 9.97 (1H, s), 8.54 (2H, m), 8.37 (1H, d), 8.10 (1H, br), 7.44 (2H, d), 7.37 (1H, dd), 7.27 (1H, dd), 7.22 (1H, dd), 7.18 (3H, m), 7.06 (1H, t), 6.92 (2H, d), 6.61 (2H, d), 4.74 (1H, q), 4.22 (1H, m), 4.13 (1H, q), 3.76 (1H, dd), 3.48 (1H, dd), 3.29 (5H, m), 3.18-2.94 (6H, m), 2.77 (1H, q), 2.24 (2H, d), 2.13 (1H, d), 1.87 (1H, d), 1.68-1.19 (15H, m), 0.93 (1H, m).

Compound 406:

¹H NMR (300 MHz, DMSO-d₆) δ 10.01 (1H, s), 9.05 (1H, d), 8.99 (1H, dd), 8.72 (1H, dd), 8.43 (1H, d), 8.22 (2H, m), 7.59 (1H, t), 7.55 (1H, q), 7.46 (2H, d), 7.40 (2H, m), 7.22 (2H, m), 7.17 (2H, d), 4.97 (1H, m), 4.37 (1H, m), 3.51-3.28 (11H, m), 3.19 (1H, q), 3.09 (1H, m), 2.97 (2H, m), 2.71 (1H, q), 2.36 (1H, d), 2.23 (1H, d), 2.00 (1H, d), 1.68 (1H, d), 1.61 (1H, m), 1.55-1.33 (4H, m), 1.08 (1H, m), 1.00 (1H, m), 0.77 (1H, m).

Compound 528:

¹H NMR (300 MHz, DMSO-d₆) δ 12.41 (1H, br), 9.99 (1H, s), 8.50 (1H, d), 8.38 (1H, d), 8.25 (1H, d), 8.00 (1H, d), 7.46 (1H, d), 7.41-7.11 (9H), 7.06 (2H, t), 6.77 (1H, s), 4.78 (1H, m), 4.17 (3H, m), 3.24-3.08 (3H), 3.08-2.90 (3H), 2.72 (1H, m), 2.29 (2H, dd), 2.10 (3H, m), 1.95 (1H, m), 1.88-1.22 (15H), 1.79 (1H, m), 1.05 (1H, m), 0.74 (1H, m).

Compound 556:

¹H NMR (300 MHz, DMSO-d₆) δ 10.28 (1H, s), 8.56 (1H), 8.43 (1H), 8.01 (1H), 7.82 (1H), 7.47 (2H, d), 7.38 (1H, d), 7.30 (2H), 7.26-7.14 (4H), 7.10 (2H), 6.88-6.7 (2H), 5.12 (1H), 4.77 (1H), 4.44 (2H), 4.30-4.10 (2H), 4.00 (1H), 3.43 (2H), 3.24-3.00 (4H), 2.90 (1H), 2.71 (1H), 2.43 (2H), 2.27 (2H), 2.07 (2H), 1.95 (2H), 1.86-1.00 (15H), 0.76 (1H).

Example 15

Evaluation of Biological Activity

Exemplary compounds were tested for the ability to bind to and modulate IL-17 activity in one or more of the below-described assays. Experimental procedures and results are provided below.

Experimental Procedures:

A. IL-17 ELISA Assay.

ELISA I: The ability of the compounds to block binding of IL17a to its receptor, IL17R, was analyzed in a competition ELISA format. High binding 96-well plates (Costar #9018) were coated with 20 nM of recombinant human IL17a (R&D Systems #317-ILB) in PBS (0.64 µg/mL), 100 µL/well, for 30 min at 37°C followed by 5 min at 4°C. Plates were then washed in PBST (PBS/0.05% Tween-20) on a plate washer, (Biotech EL-450) blocked with protein-free blocking buffer (Thermo Scientific #37573) in 250 µL/well for 30 min on shaker at room temperature, and then washed again. Compound dilutions prepared in PBST were added into the wells in duplicates followed by the addition of IL17R/Fc (R&D Systems #177-IR) at a final concentration of 12 nM. Plates were then incubated for 30 min at room temperature on the shaker. Wells with no compound served as a positive “no competitor” control, while wells with no IL17R/Fc and no compound served as a blank negative control. After an additional PBST wash, 50 ng/mL HRP-conjugated goat anti-human Fc IgG (KPL #04-10-20) was added to the plate for 30 min at room temperature, followed by PBST wash and addition of SureBlue™ TMB (KPL #52-00-03). After the sufficient color development, the reaction was fixed by the addition of 100 µL/well 0.5 N HCl and absorbance was measured at 450 nm on Biotek plate reader. The absorbances of ‘no competitor’ control and blank control did not exceed 1.0 A.U. and 0.05 A.U. respectively.

Data were processed using BioAssay Enterprise v10.1.4 (CambridgeSoft) software. Linear OD λ450 were plotted against log concentration (x) and fitted to a 4-parameter logistic equation. IC₅₀ was calculated using positive ‘no competitor’ control data as an upper limit and blank control as a lower limit in each assay.

ELISA II:

In this version, a high binding 96-well plate (Costar #9018) was coated with 20 nM of goat anti-human IgG (KPL 01-10-02) in PBS, 100 μ L/well, for 30 min at 37° C. followed by 5 min at 4° C. The plate was then washed in PBST (PBS/0.05% Tween-20) on a plate washer, (BioTek ELx450) then blocked with protein-free blocking buffer (Thermo Scientific #37573) in 250 μ L/well for 30 min on a shaker at room temperature, and then washed again. IL17R/Fc (R&D Systems #177-IR; 10 nM in PBST, 100 μ L/well) was then added to all wells. The plate was then incubated for 30 minutes at room temperature on the shaker.

While the receptor capture step was underway, compound dilutions were prepared in PBST to a concentration of 1 μ M in 1.5 mL tubes. After the receptor capture step, the plate was washed and 50 μ L PBST was added to the wells in row B down to row H. Then, 62.5 μ L of the 1 μ M compound dilutions were added to the wells of row A. From row A, 12.5 μ L of the compound solution was removed and added to row B with mixing and this process of 5-fold dilutions was continued, by row, to row G. One of the wells in row A received only PBST (62.5 μ L) and this dilution series served as the no competitor control. Then, going up from row G to row A, 50 μ L of b-IL-17 (biotinylated human IL-17, R&D Systems #317-ILB; 20 nM) was added to all wells. Row H received 50 μ L of PBST and served as the blank row, i.e., no compound and no b-IL-17. The plate was then incubated for 30 minutes at room temperature on the shaker.

After the wash, 100 μ L Streptavidin-Horseradish Peroxidase (SA-HRP) (KPL #14-30-00) at 25 ng/mL in PBST was added to each well in the plate and the plate incubated for 30 minutes at room temperature followed by wash and 100 μ L SureBlue™ TMB (KPL #52-00-03). After sufficient color development (approx 3-6 minutes), the reaction was fixed by the addition of 100 μ L/well 0.5 N HCl and absorbance was measured at 450 nm on a BioTek Synergy 2 plate reader. The absorbances of 'no competitor' control and blank control should not exceed 1.5 A.U. and 0.06 A.U., respectively.

Data was processed using BioAssay Enterprise v10.1.4 (CambridgeSoft) software. Linear OD λ 450 were plotted against log concentration (x) and fitted to a 4-parameter logistic equation. IC50 was calculated using positive 'no competitor' control data as an upper limit and blank control as a lower limit in each assay.

B. Surface Plasmon Resonance (SPR) Analysis of Compound Interactions with IL17A

SPR analysis was carried out with a GE Healthcare (Piscataway, N.J.) Biacore X100 system. Typically, the chip (NTA Biacore Biosensor chip; GE Healthcare BR-1000-34) was first conditioned by injection of 0.35 M EDTA, which also served to remove any immobilized proteins from previous runs. Before immobilization of the recombinant 6-His-tagged IL17, the chip was washed with 0.5 mM nickel chloride in NTA buffer (10 mM HEPES buffer, 0.15 M sodium chloride, 10 μ M ethylene diamine tetraacetic acid, 0.005% v/v surfactant P20 (GE Healthcare BR-1000-54)) to form a nickel chelate on the chip. IL17 protein was immobilized onto a NTA chip through its 6-His tag. IL17A was typically injected at 0.25 μ M for 60-120 seconds, followed by a stabilization step washing with NTA+0.5% DMSO for 120 seconds or longer.

Five 2-fold or 3-fold serial dilutions of test compound were injected serially onto the chip. All steps were conducted using NTA buffer containing 0.5% v/v dimethylsulfoxide (DMSO). Compounds were diluted from stock solutions of 10 mM concentration in 100% DMSO with NTA buffer to obtain 50 μ M solutions in NTA+0.5% DMSO. Subsequent 2 \times or 3 \times

dilutions were made in NTA+0.5% DMSO. Compound was generally injected for 180 seconds followed by washing the chip in buffer alone for 120 seconds. The rate of refractive index change (RU units/time) and the maximum extend of RU change was measured during the "on" phase of analyte injection, followed by measuring the rate during the "off" phase.

Kinetic parameter fits were conducted using the Biacore SPR Evaluation Program (GE Healthcare) for 1:1 molecular binding fits, after subtracting the baseline average of 2 or more runs in which no analyte was injected. This program then reports the best fit average for the "on" rate (K_a), the "off" rate (K_d) and the dissociation constant (K_D) (Chaiken, I et al., Anal Biochem 201, 197-210 (1992)). A separate program in the Biacore SPR Evaluation Program then calculates the best fit for K_d based upon the extent of binding alone (RU units bound) at each concentration of analyte and reports the best fit K_d by best fit to a Lineweaver-Burke plot. Typically, the K_d value calculated through both means agreed within a factor of three.

The presence and activity of IL17 on the NTA chip was routinely confirmed three ways:

- 1) An increase in response units (RU) upon immobilization confirms that the IL17 was immobilized on the chip;
- 2) Anti-IL17 was also injected on the chip to confirm the presence of IL17; and
- 3) IL17R was injected onto the chip to confirm that the immobilized IL17 retained its binding activity for its receptor.

Negative controls to access specificity for compound binding were conducted by immobilizing unrelated, but his-tagged, proteins (such as cyclophilin D) and conducting the same analysis as done with IL17A.

C. Inhibition of IL17A Induced Secretion of IL6 in Human Rheumatoid Arthritis Synovial Fibroblast Cells

This assay was used to determine the extent of inhibition of IL-17A induced secretion of IL-6 in primary human rheumatoid synovial fibroblast (RASf) cells by compounds of the invention. IL-17A is known to stimulate IL-6 production in RASf cells.

Low passage (passage 2-8) Primary human RASf cells (Asterand) were maintained in maintenance medium. Cells were detached from flasks by tryptic digestion and the cell density of the suspension determined. To each well of a 96 well culture plate was added 100 μ L of seeding medium containing 50,000 cells/mL and the plate incubated overnight in a humidified 37° C., 5% CO₂ incubator. The medium was replaced with fresh assay medium and cells were incubated for additional 5 hours in a humidified 37° C., 5% CO₂ incubator prior to stimulation with recombinant human IL-17A ("rhIL-17A"). Prior to addition to cells, rhIL-17A (30 ng/mL) in assay medium was incubated with either DMSO alone, compounds, or anti-IL17 receptor antibody (3 μ g/mL) for 1 hour at 37° C. The final concentration of DMSO in all samples was 0.25%. The final concentration of compounds varied from 0.03 μ M to 25 μ M.

Immediately before stimulation, cells were washed once with fresh assay medium. Then, 100 μ L of the test samples was added in triplicate wells and the plates incubated for 20 hours in a humidified 37° C., 5% CO₂ incubator. The assay medium from each well was collected and the IL-6 concentration in cell culture supernatants was determined by ELISA either immediately or after storage at -20° C.

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A water-soluble tetrazolium salt (WST1) viability assay was immediately performed on the cells after the conditioned medium was collected using a WST1 reagent purchased from Roche. The concentration of IL-6 obtained from ELISA was normalized by the WST1 data.

D. HT-29 Cellular Assay

To test the ability of a compound of the invention to neutralize or antagonize IL-17 bioactivity, the following cell-based assay was used. IL-17 can stimulate epithelial cells and other cells to secrete GRO α . The ability of a compound of the invention to neutralize IL-17-induced GRO α secretion from the human colorectal adenocarcinoma epithelial cell line HT-29 is tested in this assay.

HT-29 cells (human colorectal adenocarcinoma epithelial cells, ATCC #HTB-38), were maintained in culture/assay medium in tissue culture-treated flasks using standard techniques. HT-29 cells were grown in tissue culture flasks until they were 50-80% confluent on the day before the assay. The day before the assay, the cells were detached from the culture flasks with trypsin+EDTA. The trypsin was inactivated with complete assay medium. HT-29 cells were then centrifuged at 500 \times g for 5 minutes at room temperature. The cell pellet was then re-suspended in Defined Keratinocyte SFM (Invitrogen #10766019)+10% FCS and 50,000 HT-29 cells (in 100 μ L) were added to each treatment well of the 96-well plates. The 96-well plates were placed in a tissue culture incubator (37 $^{\circ}$ C., 5% CO $_2$) overnight. The next day, the media was removed from the cells and the cells were washed twice with Defined Keratinocyte SFM. In a separate 96-well plate, compounds to be tested were serially diluted in Defined Keratinocyte SFM and run in triplicate in 100 μ L total volume. To these compound samples were then added 100 μ L of human IL-17 at a concentration of 20 ng/mL in Defined Keratinocyte SFM for serum-free assays. 150 μ L of the compound/IL-17 mixture was then added to the cells from which the media has previously been removed. The cells were grown for 48 hours in Defined Keratinocyte SFM in a tissue culture incubator (37 $^{\circ}$ C., 5% CO $_2$).

At the end of the incubation, the plates are centrifuged (500 \times g for 5 minutes at room temperature), and the cell culture media is transferred to polypropylene 96-well plates. The supernatant was used neat in the ELISA. GRO α levels are measured with a GRO α sandwich ELISA (R+D Systems DuoSet #DY275E), as per the manufacturer's instructions. The ELISA plates were previously coated with mAb 275 (R+D Systems) at 4 μ g/mL. GRO α is detected using biotinylated goat anti-human GRO α (R+D Systems BAF275) at 200 ng/mL using TMB as a substrate. At the end of the ELISA reactions, plates are read at 450 nm on a microplate reader and compared to a standard calibration curve.

The results of the biochemical and cellular assays are set forth in Table 3 below. For each of the ELISA, SPR and RASF assays, "A" indicates a value of less than 100 nM; "B" a value of between 100 nM and 1 μ M; "C" a value between greater than 1 μ M and 10 μ M; and "D" a value of greater than 10 μ M. For the HT-29 assay, "A" indicates a value of less than 1 μ M; "B" a value of between 1 μ M and 10 μ M; "C" a value greater than 10 μ M. For every assay, a "*" indicates that some binding or activity was observed, but compound concentration was not taken high enough to calculate an IC $_{50}$ value. Blank cells indicate that the compound was not tested in that particular assay. Some compounds appear more than once in the Table below because they were tested in more than one run in one or more assays.

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TABLE 3

Assay Results for Select Compounds of Formula I						
	Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
5	100			*		
	101			C		*
	101			C		
	102			D		
10	103			D		
	104			C		
	105			C		*
	105			B		
	106	B		B	D	C
	106			B		
15	107			B		C
	107			B		
	108			A		B
	108			A		B
	109			B		B
	110			B		C
20	111			B		
	112			A		B
	113			B		C
	114			B		
	115			B		
	116			B		
	117			B		
25	118			B		
	119			B		
	120			*		B
	121			B		
	122	C		C	C	
	123	*		C	*	
30	124			B		
	125			B		
	126			B		
	127			B		
	128			B		
	129			*		
35	130			*		
	131			*		
	132			*		
	133			*		
	134			B		
	135			B		
40	136			A		
	137			B		
	138			B		
	139			B		
	140			B		
	141			A		B
	142			A		B
45	143	A		A	C	A
	144	A		A	C	B
	145			A		
	146			A		
	147			B		
	148			B		
50	149			A		
	150			A		
	151			A		
	152			B		
	153	A		A	C	
	154			A		
55	155			A		
	156			A		
	157			A		
	158	A		A		
	159	A		A	C	A
	159	A		A	C	
60	159	A		A		
	160			A		
	161			A		
	162			A		
	163			A		
	164	A		A		
	165			A		
65	166			A		
	167			A		

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TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
168			A	C	
169	B		A	D	
170			A		
171			A		
172			A		
173			A		
174			B		
175			B		
176			B		
177			A		B
178			B		
179		A	B		
180	A		A		A
181	A	A	A	C	A
182			B		
183	C		B		
184			A		B
185	A		A	C	B
185	A		A	C	
186	A	A	A	C	
187	A		A		B
188	C		B		
189			A		
190			B		
191	A		A	C	A
192	A		A	C	
193	B		A	*	
194	A	A	A	B	
195	B	A	B		
196	A		A		
197			B		
198	A		A	C	
199	A		A		
200	B		B		
201	B		A	D	
202	A		A		
203	A		A		
204	B		A		
205	A		A		
206	A		A	C	
207	B		A		
208			A		
209	A		A	C	
210			A		
211	A		A	C	
212	B		B		
213	D		B		
214	A		A	*	
215			A		
216	A		A	C	
217	A		*		
218	A	A	*	A	
219	B		*		
220	B		*		
221	C		B		
222	A		A	*	
223	A		A		
224	C		B		
225	C		B		
226	A	A	A	C	
227	B		A	C	
228	A		A	*	
229	A		*		
230	A		A		
231	*	B	B		
232	C		B		
233	B		A		
234	B				
235	B				
236	A			C	
237	A				
238	C				
239	A				
240	A				
241	B				

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TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
242	A				D
243	*				
244	B	A			
245	C				
246	A	A			D
247	B				
248	A				
249	A				
250	A				
251	B				C
252	C				
253	B				C
254	C				D
255	C				
256	D				
257	B				
258	C				
259	B	A			
260	A				C
261	A				C
262	A				
263	A				C
264	A	A			B
265	A				
266	A	A			B
267			B		
268			A		
269			A		
270	C				
271	C				
272	B				
273	B	A			C
274	A	A			B
275	B				
276	C				
277	B				
278	C				
279	A				
280	A				
280	A	A			
281	A				
282	A				
283		B			
284	B				
285	A				
286	B				
288	A	A			A
289	C				
290	B				
291	C				
292	B	A			B
292		A			C
293	B	A			C
294	A				
295					
296	A				
297	A				
298	A				
299	C				
300	B				
301	C				
302	A	A			B
303	B				
304	B				
305	A	A			B
306	B				
307	A				
308	B				
309	B				
310	B	A			
311	B	A			
312	B	A			
313	B	A			*
314	B	A			
315	C	*			

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TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
316	A	A		B	5
317	A				
318	B				
319	B				
320	B				
321	B				10
322	B				
323	B				
324	B				
325	A	A			
326	B				15
327	A				
328	B				
329	B				
330	B				
331	B				20
332	B	A		C	
333	B	A			
334	C	*			
335	B	A			
336	B	A		B	25
337	B				
338	B	A		D	
339	A	A		B	
340	A	A		B	
341	A	A		A	30
342	B	A		B	
343	B				
344	C	B			
345	B	A			
346	C	A			35
347	B	A			
348	C	B			
349	C	A			
350	*	B			
351	B				40
352	C			D	
353	B	A		C	
354	B	A			
355	C	A			
356	B	A			45
357	B	A			
358	B	A			
359	C	A			
360	B	A			
361	B	A		C	50
362	C	B			
363	*	B			
364	B	A			
365	*	A			
366	*	B			55
367	A	A		A	
368	B	A		B	
369	A	A		A	
370	B	A			
371	*	C			60
372	C	B			
373	A	A			
374	A	A			
375	B	A			
376	B	A			65
377	A	B			
378	B	A		B	
379	C	A			
380	A	A		B	
381	B	A			65
382	B	A			
383	*	C			
384	B	A			
385					
386		A		C	65
387		A		*	
388		A		A	
389		*			
390					
391		A			

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TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
392		A			
393		A			
394		A			
395		A			
396		A			
397		A			
398		A		*	
399		A		C	
400		A			
401		A			
402		A			
403		A			
404		A			
405		A		B	
406		A		C	
407		B			
408		A		B	
409		B			
410		B			
411		A			
412		B			
413		A		D	
414					
415		B			
416		A			
417		B		*	
418		A			
420		B		*	
421		C			
422		C			
423		C			
424		A		D	
425		A		B	
425		*			
426		B			
427		A		C	
428		A			
429		A			
430		A			
431		A			
432		A			
433		A			
434		A		B	
435		A			
436		B			
437		B		C	
438		A		B	
439		A		B	
440		B			
441		A		B	
442		A		C	
443		A		B	
444		A			
445		A			
446		A		B	
447		A			
448		B			
449		B			
450		A			
451		A			
452		C			
453		A		B	
454		C			
455		A		A	
456		B			
457		A		C	
458		C			
459		A			
460		A			
461		A			
462		A			
463		A			
464		A			
465		A		*	
466		A			

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TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
467		A			5
468		A			
469		A		C	
470		A		B	
471		B			
472		A			10
473		A		B	
474		A		B	
475		A		B	
476		A		B	
477		A			15
478		A		C	
479		A		A	
480		A		C	
481		B			
482		A			20
483		A			
484		A		B	
485		A			
486		A			
487		A		A	25
488		A		C	
489		A			
490		A		C	
491		C			
492		B			30
493					
494		A		B	
495		A		C	
496		A			
497		A		C	35
498		C			
499		A		B	
500		A			
501					
502		A		C	40
503		C			
504		B			
505		C			
506		*			
507		A		C	45
508		B			
509		B			
510		B			
511		A			
512		A		B	50
513		A		B	
514		B			
515		A		A	
516		D			
518		A			55
519		A			
520		A			
521		A			
522		A		C	
523		*		*	60
523		*			
524		A			
525		A			
526		B			
527		A			65
528		A		A	
529		A		A	
530		A			
531		B			
532		B			60
533		B			
534		A			
535		A		C	
536		A		B	
537		A			65
538		B			
539		A		C	
540		A		C	
541		A			

110

TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
542		A			
543		A			
544		A			
545		A			
546		B			
547		B			
548		A			
549		A		A	
550		A		C	
551		A		C	
552		A		A	
553		A		B	
554		A		*	
555		A		A	
556		A		A	
557		B			
558		A		*	
559		A			
560		A		A	
561		A		C	
562		A		C	
563		B			
564		B			
565		A			
566		A		B	
567		A		B	
568		A			
569		A			
570		A			
571		A		C	
572		A			
573		A			
574		A			
575		A			
576		A			
577		A			
578		A			
579		A			
580		A			
581		A			
582		A		C	
583		A			
584		A		C	
585		A			
586		A			
587		A			
588		A			
589		A			
590		A			
591		A			
592		B			
593		A		B	
594		A			
595		A			
596		A			
597		A			
598		*			
599		A			
600		A		C	
601		A		C	
602		A			
603		A			
604		A			
605		A			
606		D			
607		D			
608		D			
609		D			
610		D			
611		A			
612		A			
613		A			
614		A			
615		A			
616		A			

111

TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
617		A			
618		A			
619		A			
620		A			
621		A			
622		B			
623		A			
624		D			
625		B			
626		A		B	
627		A		B	
628		A			
629		A			
630		A			
631		A			
632		B			
633		A			
634		A			
635		A			
636		A			
637		A			
638		A			
639		A		C	
640		A			
641		A			
642		A			
643		A			
644		A			
645		A		B	
646		A		C	
647		A			
649		A			
650		A			
651		A			
652		B			
653		A		C	
654		A			
655		A			
656		A		A	
657		A		A	
658		A		A	
659		A			
660		A		A	
661		A		A	
662		A		A	
663		A			
664		A			
665		A			
666		A			
667		A			
668		A			

112

TABLE 3-continued

Assay Results for Select Compounds of Formula I					
Cmpd No.	ELISA I	ELISA II	SPR	RASF	HT-29
669		A			
670		A			
671		A			
672		A			
673		A			
674		A			
675		A			
676		A			
677		B			
678		A			
679		A			
680		B			
681		A			

E. Murine Model of Delayed Hypersensitivity

We used a murine model of fluorodinitrobenzene (DNFB)-induced ear edema to test the anti-inflammatory activity of both orally dosed and intraperitoneally dosed exemplary compounds of the invention. BALB/c mice (Harlan Sprague-Dawley, Inc., male, 6-8 weeks old) were topically treated on their shaved abdomen with 30 μ L of 0.5% 1-fluoro-2,4-dinitrobenzene (DNFB) (4:1 acetone:olive oil) once on Day 0 and once on Day 1.

For oral dosing ("PO"), exemplary compounds of the invention were either suspended at 3 mg/mL in 20% Cremophor EL (Sigma) (20:80; Cremophor:water) or dissolved at 1 mg/mL or 3 mg/mL in D- α -tocopherol polyethylene glycol 1000 succinate (TPGS; Sigma)/PEG-400/water (20:60:20). For intraperitoneal dosing ("IP"), exemplary compounds of the invention were dissolved in DMSO at a concentration of 5 mg/mL. On day 7, the test compound was administered (PO at either 10 mg/kg or 30 mg/kg; IP at 1, 3, or 10 mg/kg) to DNFB-treated mice. Commercially available anti-mouse IL-17A (BioLegend) administered intraperitoneally at 5 mg/kg in PBS was used as a positive control. Thirty minutes later, 20 μ L of 0.2% DNFB was applied to the right ear of animals and vehicle (DNFB:olive oil) was applied to the left ear. One and four hours after DNFB challenge, a subset of mice was exsanguinated and plasma prepared from the blood. Twenty-four hours after challenge, the remaining mice were euthanized, and their ears were removed and weighed to determine the amount of edema. Plasma was assayed for interleukin-6, TNF- α , CXCL1, and interferon- γ concentrations using commercially-available assays. The results are shown in FIGS. 1-5 and summarized in Table 4, below.

TABLE 4

Delayed Hypersensitivity Assay Results for Select Compounds of Formula I							
Cmpd No.	Route	Dose (mg/kg)	IL6 Reduction (%)	IFN γ Reduction (%)	CXCL1 Reduction (%)	TNF α Reduction (%)	Reduction in edema (%)
159	po	10	29.8	24.2			19.0
	po	30	58.3	64.5			53.7
465	po	30	42.5	47.4			23.5
453	po	3	9.3	29.2	-17.0		7.7
	po	10	35.9	35.6	31.0		36.7
	po	30	66.5	67.7	64.3		66.7
474	po	3	6.5	9.3	25.9		9.7
	po	10	22.5	29.5	44.6		23.1
	po	30	70.8	82.9	87.0		67.3
475	po	10	29.7	11.3	61.4		19.2
	po	30	51.9	45.0	63.0		49.5
159*	ip	10		28.5		21.7	54.1
	ip	10	78.6	82.2			54

TABLE 4-continued

Delayed Hypersensitivity Assay Results for Select Compounds of Formula I						
Cmpd No.	Route	Dose (mg/kg)	IL6 Reduction (%)	IFN γ Reduction (%)	CXCL1 Reduction (%)	TNF α Reduction (%)
181	ip	3	72.2	85.5		
	ip	1	62.6	54.2		
	ip	10		38.9		25.5
						Reduction in edema (%)
						44
						17
						50.1

*Compound 159 was tested in this assay on two separate occasions.

FIG. 1 demonstrates that Compounds 159 and 181 administered i.p. at 10 mg/kg both produced a statistically significant reduction in TNF- α , IFN- γ and edema as compared to a PBS control or DMSO control. FIG. 2 demonstrates that Compound 159 administered i.p. at 1 mg/kg, 3 mg/kg, or 10 mg/kg, produced a statistically significant reduction in IL-6, IFN- γ and edema compared to a DMSO control. FIG. 3 demonstrates that Compound 453 in a 20% Cremophor vehicle demonstrated an effective, dose-dependent decrease in IL-6, IFN- γ , CXCL-1, and edema when administered orally. At oral doses of 30 mg/kg, Compound 453 exhibited edema and biomarker suppression equivalent to anti-IL-17A antibody (anti-mouse IL-17 monoclonal antibody, BioLegend, Inc.) administered at 5 mg/kg (i.p.). FIG. 4 demonstrates that switching to the TPGS-PEG400 oral formulation improved the oral activity of Compound 453 relative to the Cremophor results in FIG. 3. Compound 453 administered orally at 10 mg/kg in a TPGS/PEG400/Water vehicle decreased IL-6, IFN- γ , CXCL-1, and edema as compared to any of water, 20% Cremophor vehicle alone, or TPGS/PEG400/Water vehicle alone. FIG. 5 shows that orally dosed Compound 159 in TPGS/PEG400/Water vehicle effectively reduced IL-6, IFN- γ , and edema in a dose-dependent manner.

F. Mouse Collagen-Induced Arthritis Model

Exemplary compounds of the invention were evaluated in a murine CIA model. DAB-1 mice (10/group) were anesthetized with Isoflurane, shaved at the base of the tail, and injected intradermally with 150 μ L of Freund's Complete Adjuvant (Sigma) containing bovine type II collagen (Elastin Products, Owensville, Mo.) (2 mg/mL) at the base of the tail on day 0 and again on day 21. On study days 24-25, onset of arthritis occurred and mice were randomized into treatment groups. Randomization into each group was done after swelling was obviously established in at least one paw (score of 1), and attempts were made to ensure approximately equal mean scores of 0.25 across the groups at the time of enrollment. Once a day oral treatment with 10 or 30 mg/kg of test compound in 20% Cremophor EL was initiated after enrollment and continued once a day as indicated through arthritis day 10. Mice were terminated on day 11. Clinical scores were calculated for each of the paws (right front, left front, right rear, and left rear) on arthritis days 1-11 and the results were summarized as a reduction in clinical arthritis score for all paws over the time period of dosing.

As shown in FIG. 6, Compound 453 administered orally at 30 mg/kg in 20% Cremophor EL reduced mean Clinical Arthritis Score over time as compared to the vehicle control. FIG. 7 shows that this reduction was 11%. FIG. 8, however, suggests that Compound 453 administered orally at 30 mg/kg in 20% Cremophor EL had little effect on histological parameters. The overall effect on histological parameters was 5% as shown in FIG. 9. FIG. 10 demonstrates that Compound 159 administered orally at 10 and 30 mg/kg in 20% Cremophor EL demonstrated superior reduction in mean Clinical Arthri-

tis Score on days 27-30 as compared to either TPGS/PEG400 vehicle control or 20% Cremophor EL vehicle control. FIG. 11 shows that Compound 159 reduced the overall mean Clinical Arthritis Score by 6% at 10 mg/kg and 11% at 30 mg/kg.

INCORPORATION BY REFERENCE

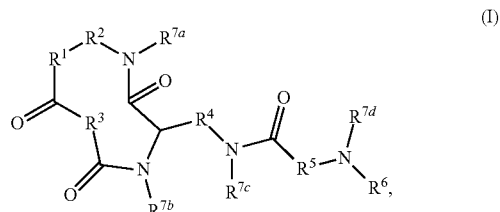
The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound represented by Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is selected from —O— and —N((C₀-C₃ alkylene)-Q)-, wherein

Q is selected from hydrogen, —N(R^{7e}), —OH, —O—C₁-C₄ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

the alkylene portion of R¹, if present, is optionally substituted; and

when the —C(O)— group adjacent to R¹ is bound directly to an —N(R^{7b})— in R³, R¹ is additionally selected from —CH₂—;

R² is an optionally substituted C₃-C₁₂ alkylene, optionally substituted C₃-C₁₂ alkenylene, or optionally substituted C₃-C₁₂ alkynylene, wherein:

up to three methylene units of R² are optionally and independently replaced with —O—, —N(R^c)—, —S—, —S(O)—, or —S(O)₂—, wherein

R^c is selected from hydrogen, C₁-C₄ alkyl, —C(O)—C₁-C₃ alkyl, —C(O)—(C₁-C₃ alkylene)-aryl, —C(O)—

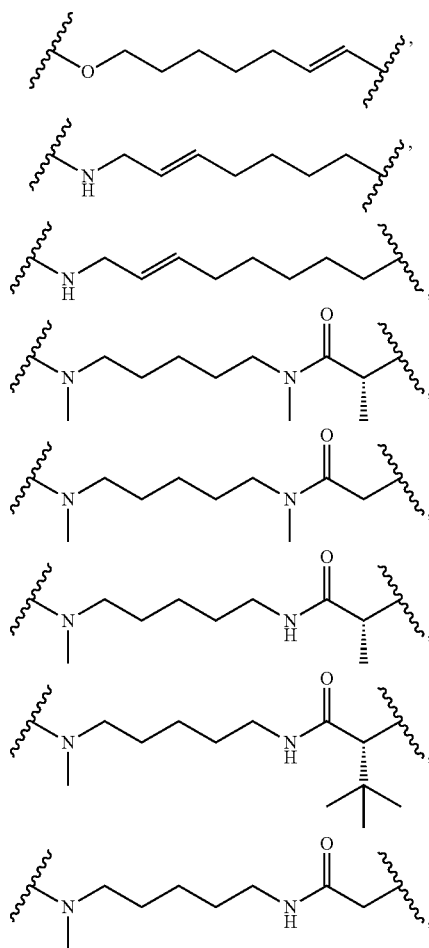
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(C₁-C₃ alkylene)-heteroaryl, —C(O)—O—C₁-C₃ alkyl, —C(O)—O—C₁-C₃ alkenyl, —S(O)₂—C₁-C₃ alkyl, —S(O)₂—(C₁-C₃ alkylene)-aryl, and —S(O)₂—(C₁-C₃ alkylene)-heteroaryl; or
 when R¹ is —N((C₀-C₃ alkylene)-Q)-, R^c is optionally taken together with R¹ and any intervening atoms to form a heterocyclyl;
 any two substituents bound to a common carbon atom in R² are optionally taken together to form =O, carbocyclyl, or heterocyclyl;
 any two substituents bound to different carbon atoms in R² are optionally taken together with any intervening atoms to form an aryl, heteroaryl, carbocyclyl, or heterocyclyl;
 any two R^c are optionally taken together with the nitrogen atoms to which they are bound and any intervening atoms to form a heterocyclyl; and
 any substituent bound to a carbon atom in R² is optionally taken together with any one R^c or with R^{7d} and any intervening atoms to form heteroaryl or heterocyclyl;
 R³ is —[C(R^d)(R^d)]_p—[N(R^{7h})]₀₋₁—[C(R^d)(R^d)]_q—, wherein:
 each R^d is independently selected from hydrogen and a suitable alkylene substituent; and any two R^d are optionally taken together with any intervening atoms to form aryl, heteroaryl, carbocyclyl, or heterocyclyl;
 p is 0, 1 or 2;
 q is 0, 1 or 2; and
 p+q is 2 or more;
 R⁴ is —[C(R^e)(R^e)]_n—Y—[C(R^e)(R^e)]_m—, wherein:
 each R^e is independently selected from hydrogen and a suitable alkylene substituent;
 Y is selected from aryl, heteroaryl, carbocyclyl, heterocyclyl, and optionally substituted C₁-C₃ alkylene;
 each of n and m are independently selected from 0, 1, 2, 3, 4, 5, and 6; and
 n+m is 6 or less;
 R⁵ is C₁-C₂ alkylene substituted with one or more —(C₀-C₅ alkylene)-R^f, wherein each R^f is independently selected from —CH₃, —O—C₁-C₃ alkyl, aryl, heteroaryl, carbocyclyl, and heterocyclyl;
 R⁶ is selected from heteroaryl, —CH₂-aryl, —C(O)—R⁸, —C(O)—O—R⁸, —C(O)—C(O)—R⁸, —S(O)—R⁸, —S(O)₂—R⁸, C(O)—N(R^{7f})—R⁸, and —S(O)₂—N(R^{7f})—R⁸;
 each R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} is independently selected from hydrogen and C₁-C₄ alkyl;
 R^{7h} is independently selected from hydrogen, C₁-C₄ alkyl, phenyl, and benzyl;
 R⁸ is selected from —(C₀-C₆ alkylene)-aryl, —(C₀-C₆ alkylene)-heteroaryl, —(C₀-C₆ alkylene)-carbocyclyl, —(C₀-C₆ alkylene)-heterocyclyl, and C₁-C₆ alkyl, wherein
 when R⁸ is C₁-C₆ alkyl, up to two methylene units in the alkyl are optionally and independently replaced with —O—, —N(R^{7g})—, —S—, —S(O)—, or —S(O)₂—; and
 any alkyl or alkylene portion of R⁸ is optionally substituted with an appropriate alkyl or alkylene substituent other than =O; or
 R^{7d} and R⁶ are optionally taken together to form a heterocyclyl; and
 any aryl, heteroaryl, carbocyclyl, or heterocyclyl portion of the compound is optionally substituted.

2. The compound of claim 1, wherein R¹ is selected from —O—, —N(H)— and —N(CH₃)—.

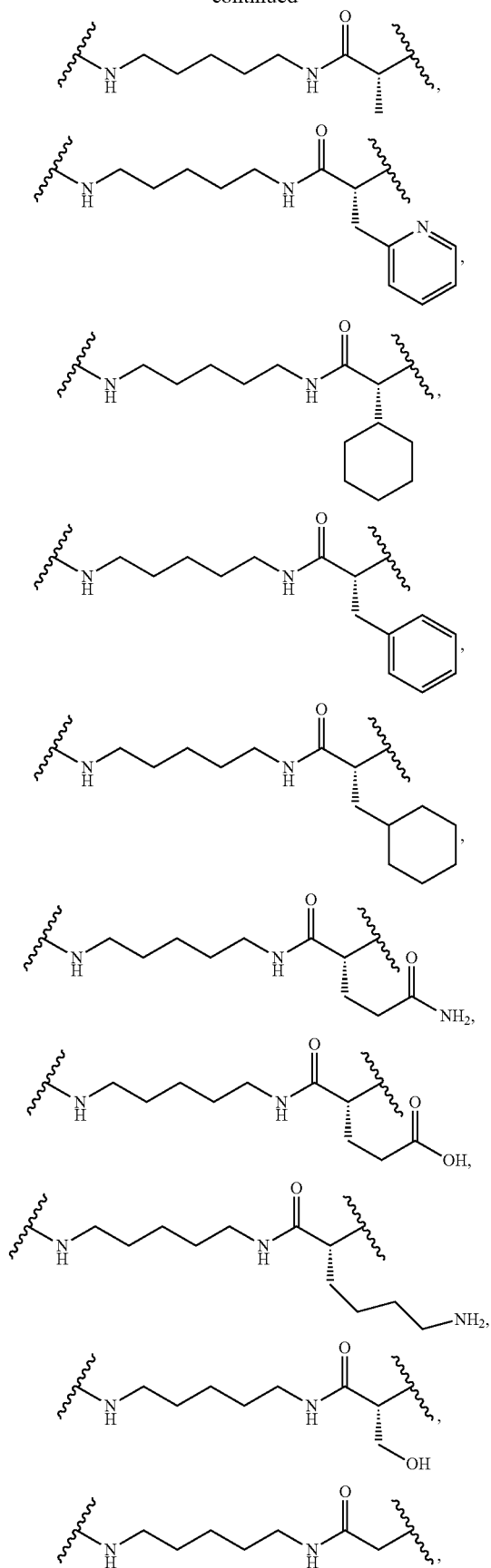
116

3. The compound of claim 1, wherein R² is selected from *—CH(R¹⁰)—Z— and *—C(H)(R¹⁰)—X—C(H)(R¹⁰)—N(R¹²)—C(O)—C(H)(R¹¹)—(CH₂)₀₋₂—, wherein:
 X is selected from —CH₂—O—CH₂—, —CH₂—N(H)—CH₂—, —CH₂—N(CH₃)—CH₂—, —CH₂—, —(CH₂)₂—, and —(CH₂)₃—;
 Z is selected from C₂-C₈ alkylene, C₂-C₈ alkenylene, or C₂-C₈ alkynylene, wherein up to 2 methylene units in Z are optionally and independently replaced with —O—, —N(H)— or —N(CH₃)—;
 each R¹⁰ is independently selected from hydrogen and —(R)—COOH, wherein at least one R¹⁰ is hydrogen;
 R¹¹ is selected from hydrogen, (S)—CH₂OH, (S)—CH₃, (S)—C(CH₃)₃, (S)-benzyl, (R)-benzyl, (S)—CH₂-pyridinyl, (S)-cyclohexyl, (S)—CH₂-cyclohexyl, (S)—(CH₂)₂—COOH, (S)—(CH₂)₂—C(O)NH₂, and (S)—(CH₂)₄—NH₂;
 R¹² is selected from hydrogen and —CH₃; and
 “*” represents a terminus of R² bound to R¹.
 4. The compound of claim 1, wherein R² is selected from *—(CH₂)₃₋₉—, *—CH(COOH)—(CH₂)₂₋₈—, *—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—O—(CH₂)₂—O—(CH₂)₂—, *—(CH₂)₂—NH—(CH₂)₂—, *—(CH₂)₂—N(CH₃)—(CH₂)₂—, *—CH₂—C≡C—(CH₂)₄₋₅, and *—CH₂—CH=CH—(CH₂)₄₋₅.
 5. The compound of claim 1, wherein the portion of the compound represented by —R¹-R² is selected from:

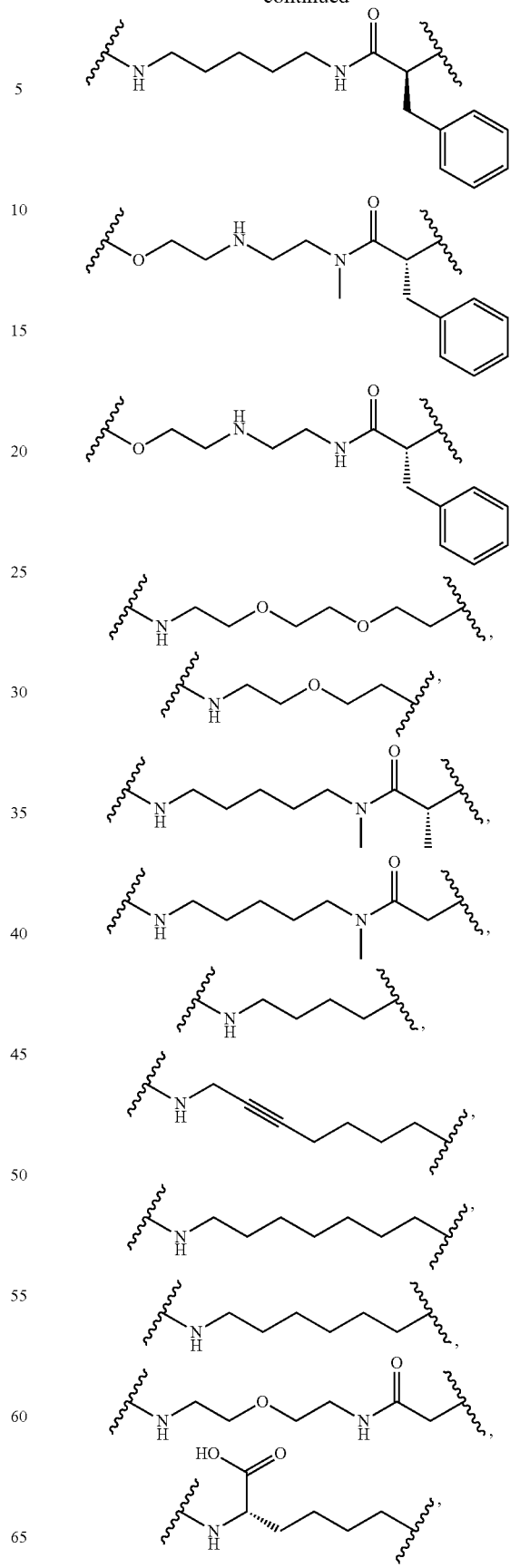


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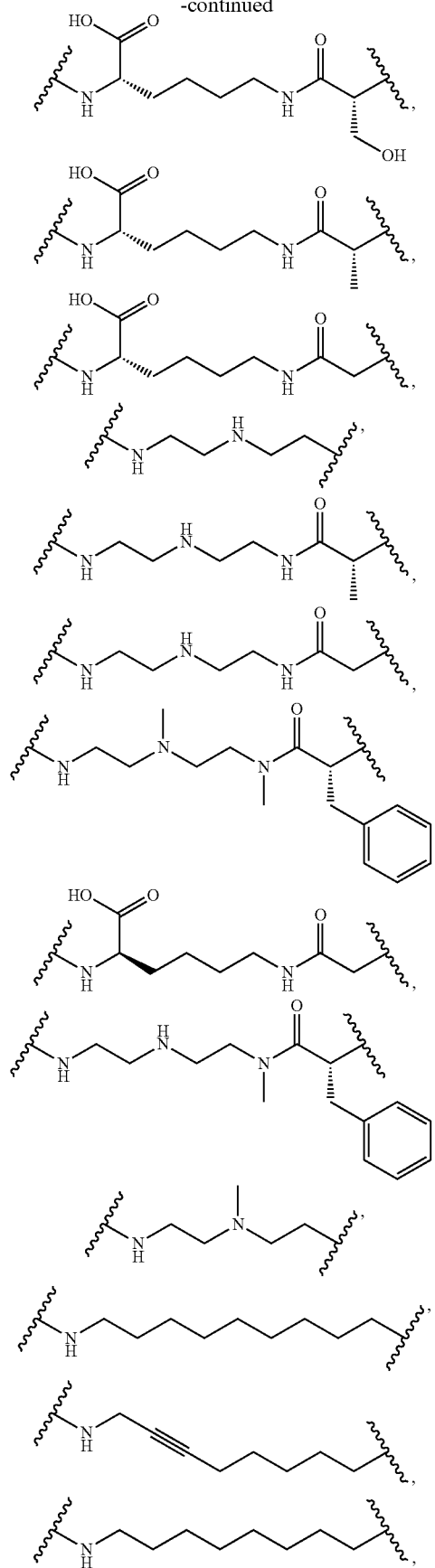
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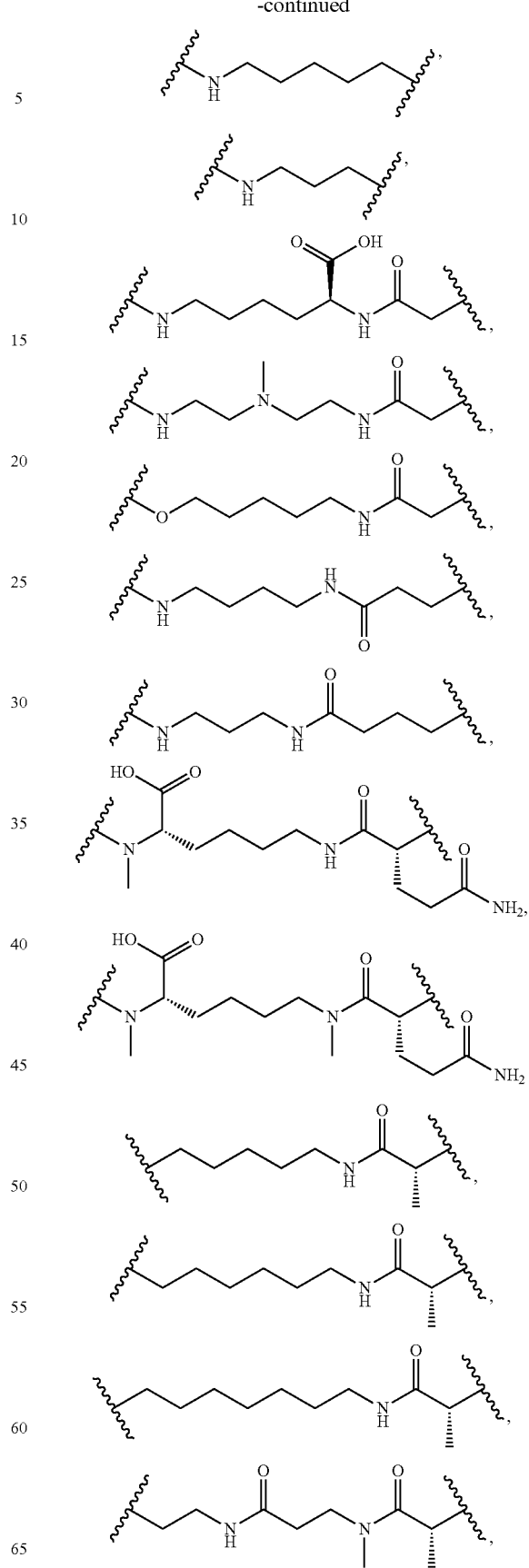
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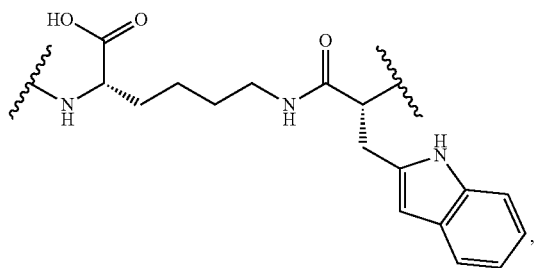
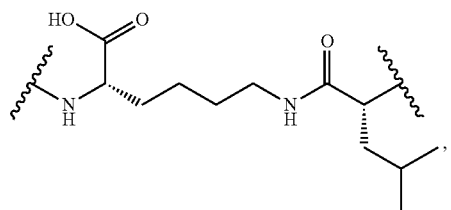
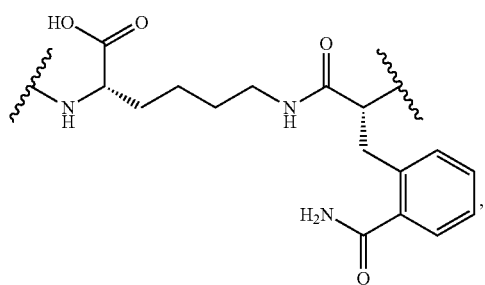
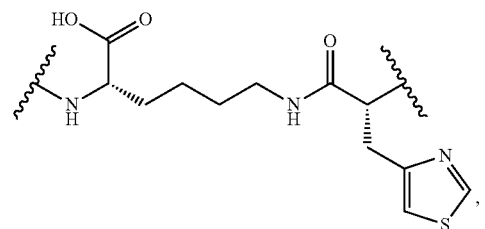
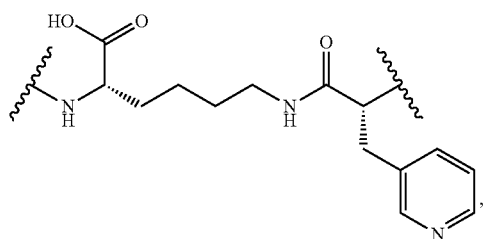
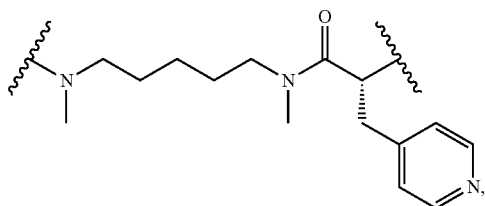
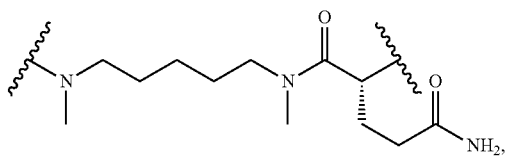
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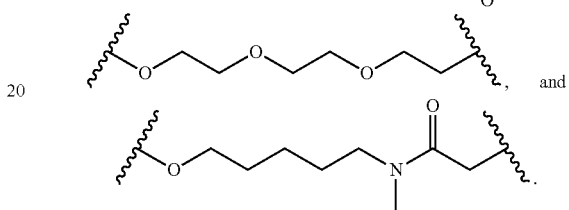
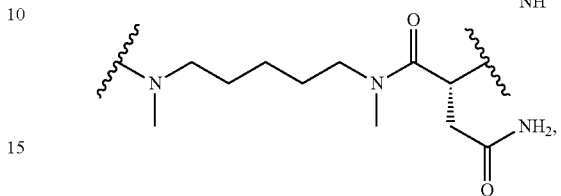
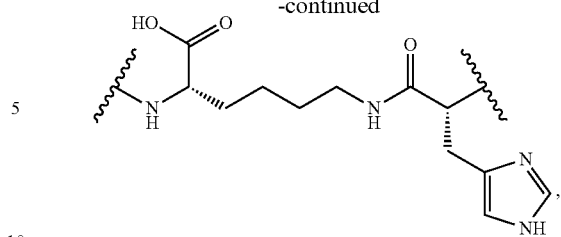


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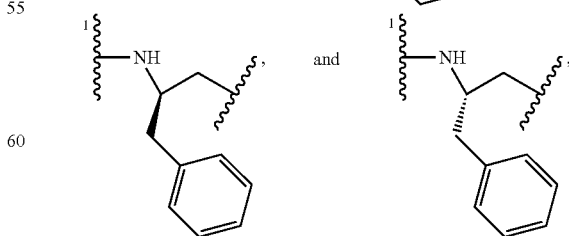
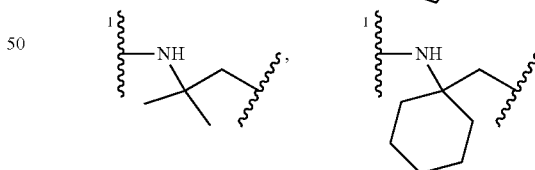
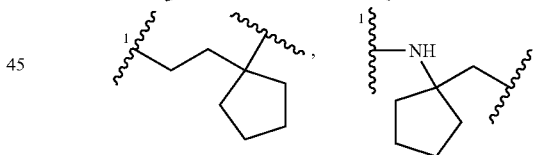
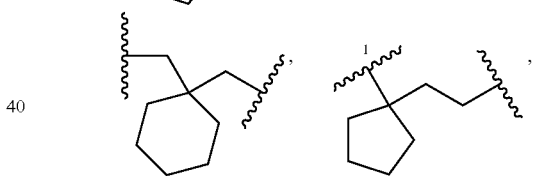
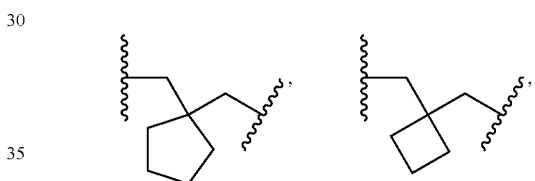
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6. The compound of claim 1, wherein R^3 is selected from $-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{CH}_3)-\text{CH}_2-$,



wherein "1" represents a portion of R^3 bound to the carbonyl moiety that is bound to R^1 .

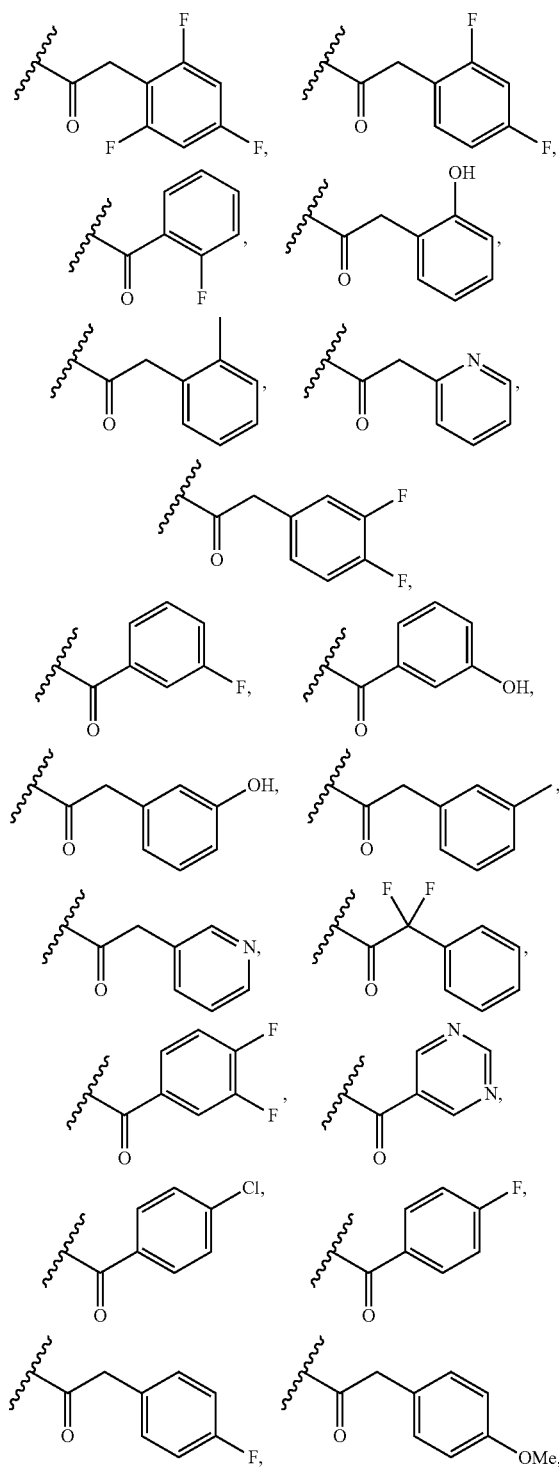
12. The compound of claim 11, wherein R^{9a} is selected from phenyl, pyridyl, quinolinyl, isoquinolinyl, cyclohexyl, 3,3-difluorocyclopropyl, —CH₃, —C(CH₃)₃, —OCH₃, —N(CH₃)₂, —N(H)(CH₃), and —N(H)-benzyl, wherein R^{9a} is optionally substituted with up to 2 substituents independently selected from fluoro, chloro, methyl, methoxy,

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hydroxy, $-\text{O}-(\text{CH}_2)_2$ -morpholin-4-yl, $-\text{O}-(\text{CH}_2)_2$ -N(CH₃)-CH₂-phenyl, and $-\text{O}-(\text{CH}_2)_2$ -N(CH₃)₂.

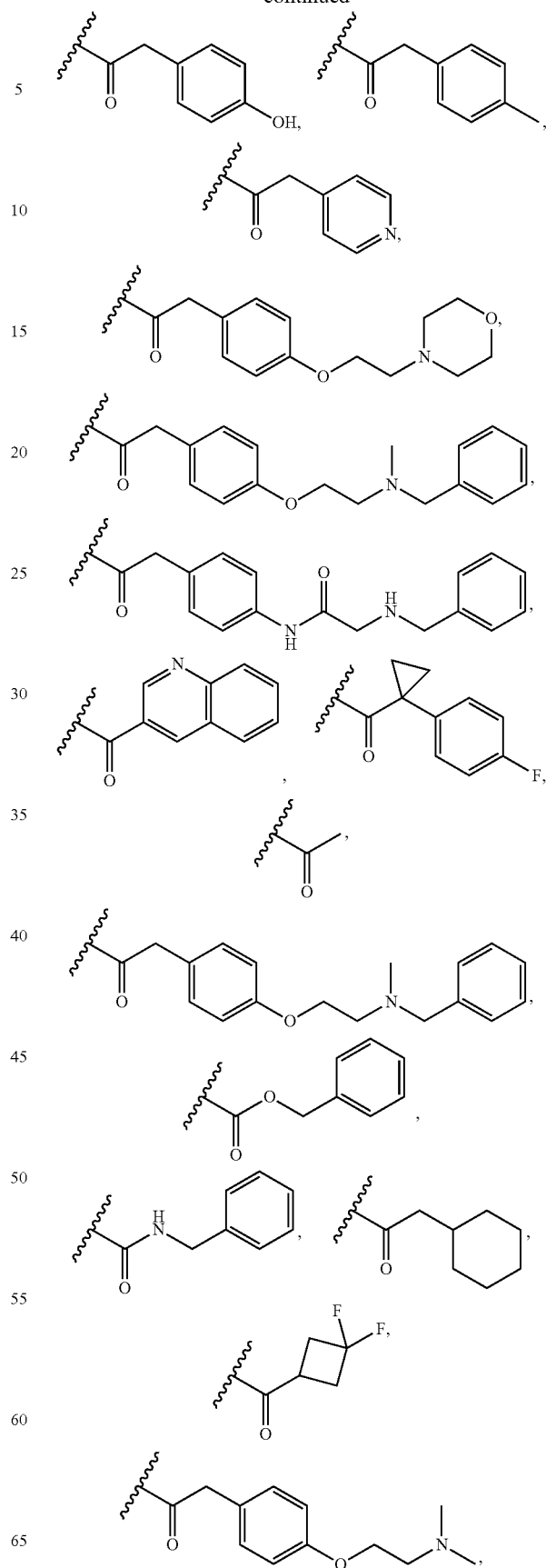
13. The compound of claim 1, wherein R⁶ is —C(O)—benzyl or —C(O)—phenyl, wherein said benzyl and phenyl in R⁶ are each optionally substituted with one or more substituents independently selected from the group consisting of halogen, hydroxyl, C₁–C₄ alkoxy, and C₁–C₄ alkyl.

14. The compound of claim 1, wherein R⁶ is selected from:



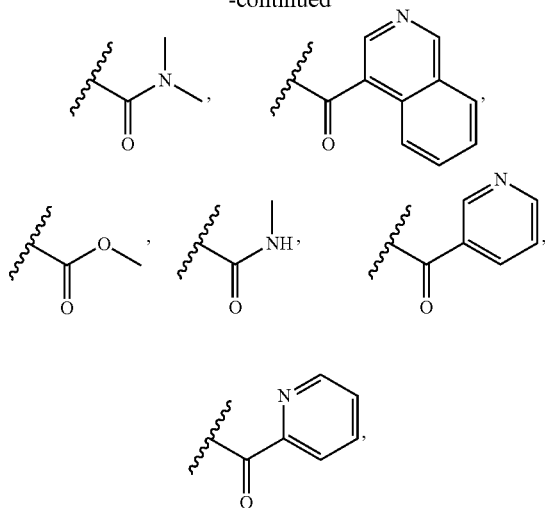
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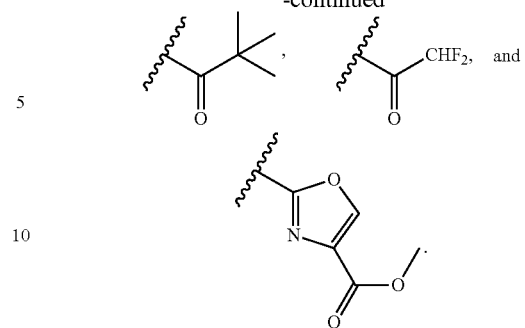


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15. The compound of claim 1, wherein R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, and R^{7g} are independently selected from methyl and hydrogen.

16. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.

* * * * *